**МИНИСТЕРСТВО ЗДРАВООХРАНЕНИЯ РЕСПУБЛИКИ БЕЛАРУСЬ**
**УЧРЕЖДЕНИЕ ОБРАЗОВАНИЯ «ВИТЕБСКИЙ ГОСУДАРСТВЕННЫЙ ОРДЕНА ДРУЖБЫ НАРОДОВ МЕДИЦИНСКИЙ УНИВЕРСИТЕТ»**

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# SKIN DISEASES AND SEXUALLY TRANSMITTED INFECTIONS

Рекомендовано Учебно-методическим объединением по высшему медицинскому, фармацевтическому образованию Республики Беларусь в качестве пособия для студентов учреждений высшего образования, обучающихся по специальности 1-79 01 01 «Лечебное дело»

**Витебск 2016**

УДК 616.5:616.97=20(042.3/.4)
ББК 55.81я7+55.83я7
А28

Р е ц е н з е н т ы:

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**Adaskevich, U.P.**
A-25 Skin Diseases and Sexually Transmitted Infections : handbook / U.P. Adaskevich. – Vitebsk: VSMU, 2016. – 396 p.

ISBN 978-985-466-830-7

This handbook is compiled for medical students engaged in learning about skin and venereal diseases and their management. It covers both common and rare but important conditions which are incorporated into the basic program on teaching dermatology and venereology at medical faculties for various medical specialties. The handbook also contains chapters about skin diseases and STDs which are common for Asia, Africa and Latin America and it can be helpful for medical students coming from these regions. We hope that it will also be of value for clinical interns and post graduate research students since the text is sufficiently detailed to be of use for those embarking on a career in dermatology and venereology. In this, second edition ofSkin Diseases and Sexually Transmitted Infections the text have been updated with particular regard to advances in treatment and provided with numerous tables of salient points for ready reference. We also hope that exposure to the handbook will prompt a deeper interest in this important medical specialty.

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# CONTENTS

# I. THE STRUCTURE AND FUNCTION OF THE SKIN, HAIR AND NAILS

The skin is one of the largest organs in the body. It has a surface area of 1.8 $m^2$ and makes up approximately 16% of our body weight. More importantly, the skin is a window through which the physician can "see" the entire body.
The skin is often referred to as the "integumentary system" composed of epithelial, mesenchymal, glandular and neurovascular components. Specifically, the integumentary system consists of the skin and its derivatives such as: sweat glands, sebaceous glands, nails, hair, and arrector pili muscles. Also included in the system are the mammary glands and the teeth.

The skin can also be divided into **three main functional areas**:
**1)** **Epidermis**: the major protective layer derived from ectoderm.
2) **Dermis**: the major support layer derived from mesoderm.
3) **Skin Appendages**: cells derived from both ectoderm and mesoderm:
- Eccrine Sweat Gland
- Apocrine Sweat Gland
- Sebaceous Gland
- Hair Follicle
- Nails

Based on the thickness of the epidermis, skin can also be classified as thick or thin:
1) **Thick skin** covers our palms and soles. It has sweat glands, but lacks hair follicles, arrector pili muscles, and sebaceous glands.
2) **Thin skin**covers most of the rest of the body. It contains hair follicles, arrector pili muscles, sweat glands, and sebaceous glands.

## 1. The Microstructureof the Skin

The skin is conventionally divided into several layers (**Fig.1.1**). Its two main layers are **the epidermis and the dermis**. The tissue immediately below the dermis is called **the subcutis**, although in certain sites (e.g. the scrotum) the skin lies directly on the muscle. The subcutis (**Fig.1.4**) consists largely of fat transversed by nerves and blood vessels.

### 1.1. The Epidermis

The epidermis is a stratified squamous epithelium that mainly serves as a protective barrier. The epidermis is about 0.1 mm thick, but on the palms and soles the thickness can be greater (0.8-1.4 mm)**.** It has **four well-defined layers (Fig.1.2)**. The principal cell of the epidermis is known as a "**keratinocyte**" but the epidermis contains also melanocytes, Langerhans's cells and Merkel cells.

Keratinocytes are produced by cell division in the deepest **basal layer** of the epidermis, the so-called stratum basale. In the process ofmaturation and differentiation they move progressively to the skin surface finally producing the surface layer of cells which is called the **hornylayer** or**stratum corneum.** These horny cells or corneocytes are then shed from the skin surface.The process of differentiation involves also two transitional phases, recognized as producing **the prickle cell** (spinous) **layer** and the **granular cell** layer respectively.
The keratinocyte "transit" time, from the beginning of normal differentiation to the final shedding from the surface, is in the order of 50-70 days. The loss of cells from the surface is matched by production in the basal layer so that epidermis thickness is constant.

**Fig.1.1. Microstructure of the Skin**

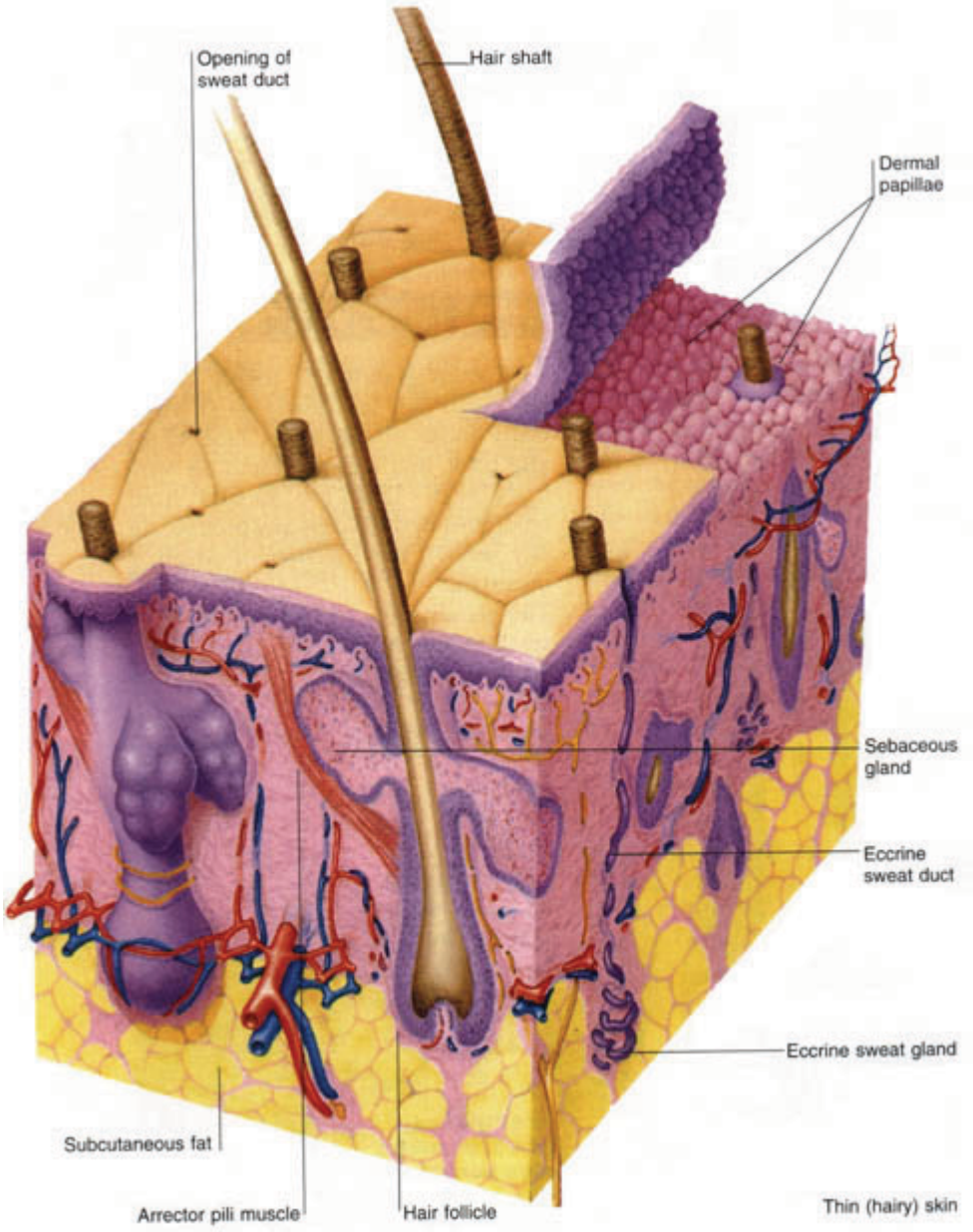
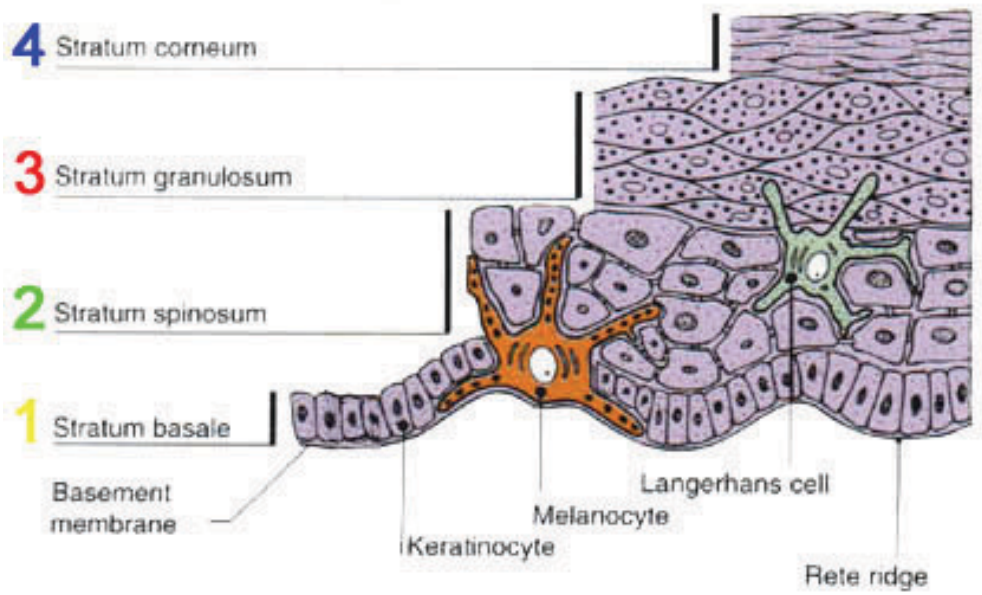


**Fig.1.2. Four Main Layers of the Epidermis**




## 1) BASAL CELL LAYER (STRATUM BASALE)

The basal cell layer is composed of columnar cells which are anchored to the basement membrane - a multilayered structure with anchoring fibrils extending into the superficial dermis. Interspersed among the basal cells are melanocytes.These large dendritic cells derived from the neural crest make up to 5-10% of the layer and are most numerous on the face and other exposed areas of the skin. They are responsible for melanin pigment production which is synthesized from tyrosine in melanosomes - cytoplasmatic organelles of melanocytes. The melanosomes migrate along the dendrites of the melanocytes, and are transferred to the keratinocytes in the prickle cell layer.

Merkel cells, although present in only very small numbers, can also be found in this layer and are closely associated with specialized nerve endings within the epidermis. Merkel cells have a role in sensation. Neuropeptide granules, neurofilaments, and keratin can be seen in their cytoplasm.

## 2) PRICKLE CELL LAYER (STRATUM SPINOSUM)

Daughter basal cells migrate upwards and differentiate into polyhedral cells in this layer. Desmosomes (intercellular bridges) interconnect these polyhedral cells and give rise to the "prickles/spines"seen at light microscope level. The desmosomes themselves are stabilized within the cells by tonofilaments. Scattered throughout the prickle cell layer are Langerhans' cells. These dendritic cells originate in the

bone marrow and migrate to the epidermis where they are the first line of immunological defense against environmental antigens.Langerhans' cells are responsible for the uptake of such antigens and their presentation to immunocompetent lymphocytes.

### 3) GRANULAR CELL LAYER (STRATUM GRANULOSUM)

In this layer, cells become flattened and lose their nuclei. Their cytoplasm contains numerous darkly staining particles known as keratohyalin granules. Also present in the cytoplasm of cells in the granular layer are organelles known as lamellar granules (Odland bodies). These contain lipids and enzymes, and they discharge their contents into the intercellular spaces between the cells of the granular layer and stratum corneum - providing the equivalent of "mortar" between the cellular "bricks" and contributing to the barrier function of the epidermis.

### 4) HORNY LAYER (STRATUM CORNEUM)

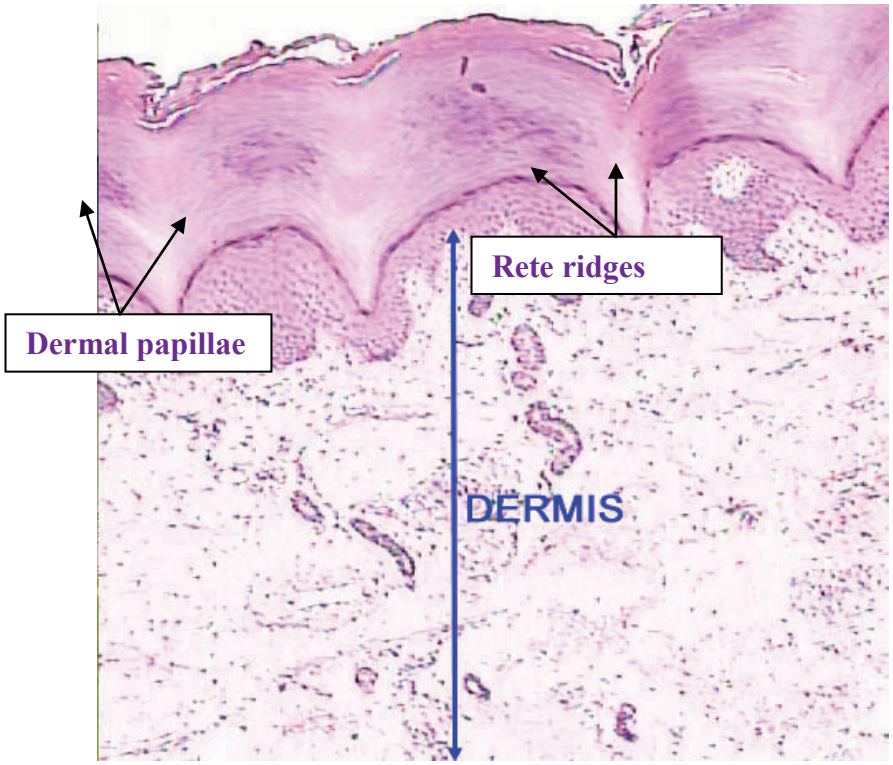
This layer is composed of sheets of overlapping polyhedral cornified cells calledcorneocytes which aredevoid of nuclei and cytoplasmic organelles. The corneocytes are keratinized dead cells that are gradually abraded by daily wear and tear. Adjacent corneocytes overlap at their margins, and this locking together of cells, together with intercellular lipid, forms a very effective barrier. The stratum corneum varies in thickness according to the region of the body. This layer is thickest on the palms and soles. The flattened corneocyte develops a thickened cell envelope. Its cytoplasm is replaced by keratin tonofibrils in a matrix formed from keratohyalin granules. The membrane-coating granules produce lipid glue that keeps the cells stuck together. This forms the hydrophobic barrier membrane that protects the skin and prevents water loss.

## 1.2. The Dermis

The dermis is a layer of connective tissue lying beneath the epidermis **(Fig.1.3)**. Itcontains numerous specialized structures and forms the bulk of the skin. The dermal thickness varies being thinnest (0.6 mm) on the eyelids and thickest (3 mm or more) on the back, palms, and soles.
The dermis and the epidermis interdigitate via downward epidermal projections (rete ridges), and upward dermal projections (dermal papillae).The main component of the dermis is a network of interlacing fibers, mostly collagen but with some elastin. They are embedded in a matrix of mucopolysaccharides (glycosaminoglicans) which impart movement to some dermal structures. Collagen fibers make up 70% of the dermis and give structural toughness and strength. Elastin fibers are loosely arranged in all directions and give elasticity to the skin. They are most prevalent near hair follicles and sweat glands and less so in the papillary dermis. The papillary part of the dermis is composed of loosely

interwoven collagen. Found deeper is the thicker reticular dermis with its coarser and horizontally running bundles of collagen.
The **main cellular elements of the dermis** are **fibroblasts, mast cells and macrophages.**
**Fibroblasts** synthesize the connective tissue matrix of the dermis and are usually found in close proximity to collagen and elastin fibers.
**Mast cells** are specialized secretory cells present throughout the dermis but more numerous around blood vessels and appendages. They contain granules whose contents include mediators such as histamine, prostaglandins, leukotrienes and eosinophil and neutrophil chemotactic factors.
**Macrophages** are phagocytic cells that originate in the bone marrow. They act as scavengers of cell debris and extracellular material
The dermis is also richly supplied with blood vessels, lymphatics, nerves and sensory receptors.

**Fig.1.3.The dermisis a layer of connective tissue lying beneath the epidermis**




## 1.3. The Basement Membrane Zone

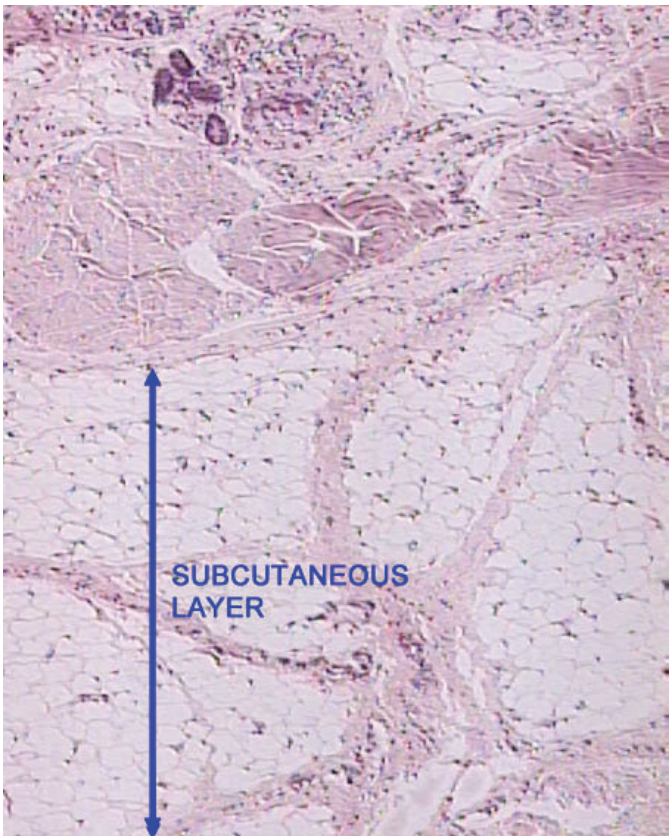
The basement membrane zone, also called the dermo-epidermal junction, is the narrow, but multilayered, structure lying between the epidermis and the dermis and supplies the cohesion between these two layers. This cohesion may be damaged by genetic defects in the proteins involved (as in some forms of epidermolysis

bullosa) or by acquired disease processes, such as bullous pemphigoid. A further degree of stability is provided by the corrugations of the basement membrane zone, in which the rete ridges of the epidermis interdigitate with dermal papillae. This occurs less often with age.

## 1.4. TheSubcutis

Beneath the dermis, a layer of subcutaneous fat separates the skin from underlying fascia and muscle (**Fig.1.4**). This subcutaneous layer consists of loose connective tissue and fat transversed by nerves and blood vessels. It can be up to 3 cm thick on the abdomen.

**Fig.1.4.The subcutis consists of loose connective tissue and fat transversed by nerves and blood vessels**




## 2. Appendageal Structures

Three important components of the skin are conventionally considered as "appendages" of the epidermis:

1) hair follicles and their sebaceous glands
2) eccrine and apocrine sweat glands and
3) the nails.

All lie within the dermis or the subcutis, but connect with the surface.

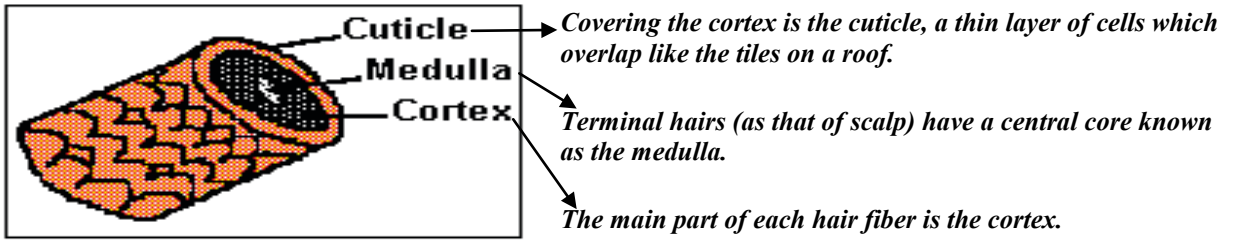
## 2.1. Hair Follicles and Sebaceous Glands (or Pilosebaceous Units)

Hairs grow out of tubular invaginations of the epidermis known as follicles, and a hair follicle and its associated sebaceous glands are referred to as a "pilosebaceous unit». There are **three types of hair** seen in humans: terminal, vellus and lanugo. Fine, soft ***lanugo*** hair is present in utero and is shed by the eighth month of fetal life. Fine, downy ***vellus*** hair covers most of the body except those areas occupied by terminal hair. Thick and pigmented ***terminal*** hair occurs on the scalp, eyebrows and eyelashes before puberty. After puberty, under the influence of androgens, secondary sexual terminal hair develops from vellus hair in the axillae and pubic region, and on the trunk and limbs in men.

The growth of each hair is cyclical. Periods of active growth alternate with resting phases. After each period of active growth (***anagen***) there is a short transitional phase (***catagen***), follows by a resting phase (***telogen***), after which the follicle reactivates, a new hair is produced and the old hair is shed. The duration of anagen in a scalp follicle is genetically determined and ranges from 2 to more than 5 years. In pubic or eyebrows hair anagen lasts a few months. Scalp hair catagen lasts about 2 weeks and telogen from 3 to 4 months. The hair cycle occurs in different hair follicles asynchronously, i.e., at a given time, each individual hair follicle is at a different stage of the hair cycle. At any one time approximately 85% of scalp hairs are in anagen, 1% in catagen and 14% in telogen. The average number of hairs shed daily is 100.
Hair follicles extend into the dermis at an angle. A small bundle of smooth muscle fibers, **the arrector pili muscle**, extends from just beneath the epidermis and is attached to the side of the follicle at an angle. Arrector pili muscles are supplied by adrenergic nerves, and are responsible for the erection of hair during cold or emotional stress ('goose flesh'). **The sebaceous gland** is attached to the follicle just above the point of attachment of the arrector pili. At the lower end of the follicle is the **hair bulb**, part of which, the hair matrix, is a zone of rapidly dividing cells which is responsible for the formation of the hair shaft. **Hair pigment** is produced by melanocytes in the hair bulb. Cells produced in the hair bulb become densely packed, elongated and arranged parallel to the long axis of the hair shaft. They gradually become keratinized as they ascend in the hair follicle and as the hair shaft matures and grows.

Ultimately the hair shaft consists of the following tubular layers (**Fig.1.5**):
– **thecortex**, which is more or less equivalent to the prickle cell layer of the epidermis, but within which keratinization is further advanced. It is mainly composed of keratinized spindle-shaped cells
– **the cuticle**, a thin layer of overlapping keratinized cells whose free margins point towards the tip of the hair
– **the medulla,** present on terminal hairs, which is a central core, consisting of specialized cells which contain air spaces

**Fig.1.5.The Hair Shaft**




The cross-sectional shape of hair varies with body site and with race. African hair is distinctly oval in cross-section, and pubic, beard and eyelash hairs are oval in all racial types. The form of scalp hair also differs among human races (e.g., the peppercorn pattern in black Africans). The average rate of growth of human scalp hair is 0.37mm per day. In women scalp hair grows faster and body hair grows more slowly than in men. The rate of growth of body hair is undoubtedly increased by androgens, since it can be reduced by treatment with antiandrogenic steroids.

***Sebaceous glands***

Sebaceous glands are found everywhere on the skin apart from the hands and feet. They are particularly numerous and prominent on the head and neck, the chest, and the back. Sebaceous glands are part of the pilosebaceous unit, and their lipid-rich product (sebum) flows through a duct into the hair follicle. They are holocrine glands – sebum is produced by disintegration of glandular cells rather than an active secretory process. Modified sebaceous glands which open directly on the surface are found on the eyelids(Meibomian glands), lips, nipples, glans penis and prepuce(Tyson's glands), and the buccal mucosa (Fordyce spots).

Sebaceous glands are prominent at birth, under the influence of maternal hormones, but atrophy soon after, and do not enlarge again until puberty. Enlargement of the glands and sebum production at puberty are stimulated by androgens. Growth hormone and thyroid hormones also affect sebum production.It should be noted that: (1) sebum production is low in children; (2) in adults, sebum production is higher in men than in women; (3) in men, sebum production falls only slightly with advancing age, whereas in women it decreases significantly after the age of 50.

**2.2. Sweat Glands**

Generalized sweating is the normal response to exercise or thermal stress by which human beings control their body temperature through evaporative heat loss. Failure of this mechanism can cause hyperthermia and death.Human skin possesses **two kinds of sweet glands: eccrine and apocrine**.

***Eccrine sweat glands***

Humans have over 2 million eccrine sweat glands distributed over nearly the entire body surface (except labia minora and glans penis). They are more numerous in such sites as the forehead, axillae, palms and soles. A person can perspire as much as several liters per hour and 10 liters per day, which is far greater than the secretory rates of other exocrine glands such as the salivary and lacrimal glands and the pancreas.

Each eccrine sweat gland consists of **a secretory coil** deep in the dermis, and **a duct** which conveys the secreted sweat to the surface. Eccrine sweat glands are innervated by the sympathetic nervous system, but the neurotransmitter is acetylholine. The secretory activity of the human eccrine sweat glands consists of **two major functions**:

(1) **secretion** of an ultrafiltrate of a plasma-like precursor fluid by the secretory coil in response to acetylcholine released from the sympathetic nerve endings, and

(2) **reabsorption** of sodium in excess of water by the duct, thereby producing a hypotonic skin surface sweat.

Under extreme conditions, where the amount of perspiration reaches several liters a day, the ductal reabsorptive function assumes a vital role in maintaining homeostasis of the entire body.

In addition to the secretion of water and electrolytes, the sweat glands serve as excretory organ for heavy metals, organic compounds, and macromolecules. The sweat is composed of 99% water, electrolytes, lactate (provides an acidic pH to resist infection), urea, ammonia, proteolytic enzymes, and other substances.

There is a hypothalamic preoptic sweat center that plays an essential role in regulation of body temperature. Sweat secretion on palms and soles is more or less continuous (perpetual sweating) when humans are awake. In contrast, those glands on the general skin surface respond predominantly to thermal stimuli (thermal sweating). Both types of sweating can be inhibited by atropine as all sweat glands in different areas of the body are stimulated by the same sympathetic cholinergic mechanism. Sweating induced by emotional stress (emotional sweating) can occur over the whole skin surface, but usually it is confined to palms, soles, axillae, and the forehead.

***Apocrine sweat glands***

The term "*apocrine glands"*was given to sweat glands present in the axillae and anogenital area which are under the control of sex hormones, mainly androgens. Specialized apocrine glands include the wax glands of the ear and the milk glands of the breast.

Apocrine glands are also composed of a secretory coil and a duct, but **the duct opens into a hair follicle, not directly onto the surface of the skin**. But nowadays by electron microscopy, these apocrine glands (apocrine = apical part of the cell is destroyed during the process of secretion) proved to be merocrine in nature (merocrine = no destruction of the cell during the process of secretion).

The "apocrine" sweat of humans has been described as milky (because it is mixed with sebum due to shared duct) and viscid, without odour when it is first secreted. This oily secretion of apocrine glands contains protein, carbohydrate, ammonia and lipid. These glands become active at puberty, and secretion is controlled by adrenergic nerve fibers.Pungent axillary body odour (axillary bromhidrosis) is the result if the action of bacteria on apocrine secretion.

## 2.3. Nails

The nail acts as a protective covering to the end of the digit and assists in grasping small objects. It is a transparent plate of keratin derived from an invagination of epidermis on the dorsum of the terminal phalanx of a digit (**Fig.1.6**).

**Thenail plate** is roughly rectangular and flat in shape but shows considerable variation in different persons. It is the product of cell division in **thenail matrix**, which lies deep to the proximal nail fold, but is partly visible as the pale "half-moon" (lunula) at the base of the nail.

**Thelunula** is the most distal portion of the matrix and determines the shape of the free edge of the nail plate. The nail plate is firmly adherent to the underlying **nail bed**. The pink color of the nail bed results from its extensive vascular network and can be seen because of the transparency of the plate.

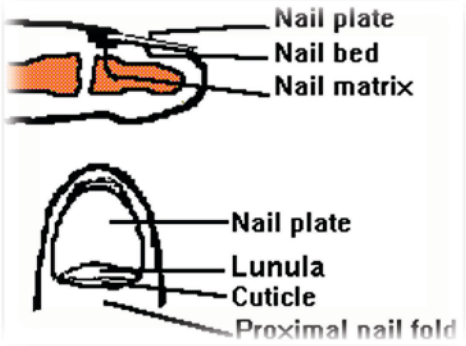
As the nail plate emerges from the matrix, its lateral and proximal borders are enveloped by folds of the skin termed **the lateral and proximal nail folds**.

The extension of the horny layer of the proximal nail fold onto the nail plate is called **the cuticle**.It forms a seal between the nail plate and proximal nail fold, preventing penetration of extraneous material.

The skin underlying the free end of the nail is referred to as **the hyponychium** and is contiguous with the skin on the tip of the finger.

Nail growth is continuous throughout life, but is more rapid in youth than in old age as well as during pregnancy, in case of nail biting, trauma andduring regrowth after avulsion. The average rate of growth of fingernails is approximately 1 mm per week, and the time taken for a fingernail to grow from matrix to free edge is about 6 months. Toenails grow at one-third the rate of fingernails, and take about 18 months to grow from matrix to free edge.

**Fig.1.6.The Nail**



Many factors affect nail growth rate. It is increased in psoriasis, and may be speeded up in the presence of inflammatory change around the nail. A severe systemic upset can produce a sudden slowing in nail growth, causing a transverse groove in each nail plate. These grooves, known as Beau's lines, subsequently become visible as the nails grow out.
Nail growth may also be considerably slowed in acute viral infections such as mumps and measles, in starvation, some types of anemia as well as in the digits of a limb immobilized in plaster.

## 3. TheFunctionsof the Skin

The complex organization and structure of the skinobviously point out to the fact that the skin performs several important (sometimes vitally important) physiological functions. Some of its functions are as follows:

### Box 1.1. The functions of the Skin

**The skin:**

- **acts as a barrier to physical agents**
- **protects against mechanical injury**
- **prevents dehydration of body through fluid loss**
- **reduces the penetration of UV radiation**
- **helps regulate body temperature**
- **provides a surface for grip**
- **acts as a sensory organ**
- **acts as an outpost for immune surveillance**
- **plays a role in Vitamin D production**
- **has a cosmetic association**

### *Barrier function*

The outer layers of the epidermis consist of several overlapping plates of keratin. These are surrounded by a thin film of lipid that is dispersed across the surface of the cells by the Odland bodies (or membrane-coating granules), which become visible under electron microscopy on the prickle cell layer. The envelope thus produced is both strong and flexible, providing a semi-permeable barrier to the outside world. Thus, the skinis structured to prevent loss of essential body fluids, and makes diffusion of water into the environment very difficult. In the absence of a stratum corneum we would all lose significant amounts of water to the environment, and rapidly become dehydrated. The stratum corneum is also quite an effective barrier to the penetration of external agents and protects the body against the entry of toxic environmental chemicals. However, the barrier capacity of considerably reduces if the stratum corneum is hydrated, or its lipid content is reduced by the use of lipid solvents.

One aspect of the skin's barrier function deserves a special mention: the role of melanocytes and melanin in the **prevention of damage by ultraviolet radiation**. Melanocytes produce melanin granules at a genetically predetermined rate and transport them into the cytoplasm of surrounding keratinocytes. Melanin absorbs ultraviolet radiation and thus protects the nuclei of the basal and spinous cells from DNA damage. In the lower layers of the epidermis, the melanin granules are arranged as a shield or umbrella over the nuclei of the basal and spinous cells. In the outer layers, melanin granules are scattered throughout the cells.

***Immunological surveillance***

The skin is and important site of immunological activity and partof the innate immunity of the body against invasion by microorganisms. The dryness and constant desquamation of the skin, its normal flora, fatty acids of sebum and the lactic acid of sweat, all represent natural defense mechanisms against invasion by microorganisms.

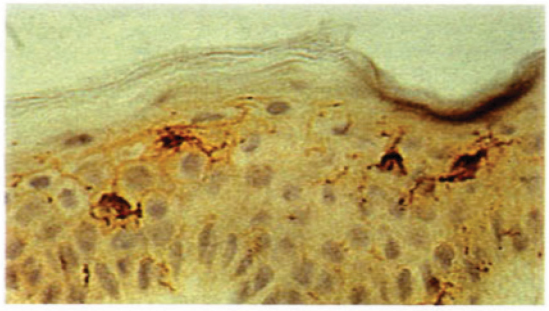
A variety of the skin cells and chemical messengers (or cytokines) produced by these cells are involved in recruiting and stimulating both cellular and humoral responses:

**Box 1.2 Skin cells involved in recruiting and stimulating both cellular and humoral responses**

- **Langerhans cells (Fig. 1.7)** present in the epidermis have an antigen-presenting capacity and might play an important role in delayed hypersensitivity reactions. They also play a role in immunosurveillance against viral infections.
- **Epidermal keratinocytes** interact with neighboring Langerhans cells and secrete a number of immunoregulating cytokines, and epidermotropic T-cells forming the skin immune system: SALT (skin associated lymphoid tissue).
- **Mast cells** in the dermis aid the process by releasing vasoactive chemicals that help in the recruitment of cells.
- **Tissue macrophages** are recruited by vessel dilatation and release of chemical attractants.
- So-called **adhesion molecules** assist by binding the surface markers on immunologically competent cells.

These functions are important in dealing with infection and tumour cells. Dysregulation leads to allergic contact dermatitis and, probably, to atopic dermatitis, psoriasis and many other skin disorders. Defective function, in patients receiving immunosuppressive drugs for example, increases the risk of infection and tumour formation.

**Fig.1.7 Langerhans Cells.**



Langerhans cells form a network in the epidermis. In this section, the Langerhans cells have been stained with a monoclonal antibody to HLA-DR

***Temperature regulation***

The skin is a vital part of the body's temperature regulation system, protecting us against hypothermia and hyperthermia, both of them may be fatal.The body core temperature is regulated by a temperature-sensitive area in the hypothalamus, and this is influenced by the temperature of the blood which perfuses it. The response of the skin to cold is vasoconstriction and a marked reduction in blood flow, decreasing transfer of heat to the body surface. The response to hear is vasodilatation, and increase in skin blood flow and loss of heat to the environment. Perspiration helps to cool the body by evaporation of sweat. These thermoregulatory functions are impaired in certain skin diseases - patients suffering from exfoliative dermatitis (erythroderma) radiate heat to their environment because their skin blood flow is considerably increased and they are unable to control this by vasoconstriction. In a cold environment their central core temperature drops, in spite of producing metabolic heat by shivering, and they may die of hyperthermia.

***Sensation***

The skin is also a huge sensory receptor, perceiving heat, cold, pain, light touch and pressure and even tickle. The same nerve fibers that carry pain also carry the sensation of itch. This sensation, which is unique to the skin, causes considerable distress when it becomes persistent and severe.Parts of the skin are considered as erogenous zones. The skin is very rich in nerve endings, especially on the fingers, toes, lips (and tongue) and this allows us to localize sensations very accurately.

***Biochemical reactions***

The skin is involved in several biochemical processes but actively participate in vitamin D and androgen metabolism. A vital part of vitamin D metabolism takes place in the epidermis: exposure to ultraviolet radiation, largely in the basal and prickle cell layers, converts 7-dehydrocholesterol to vitamin D3, vial a peculiar molecule, previtamin D3. Without this natural process, vitamin D3 deficiency

leads to impaired intestinal calcium and phosphate absorption, which results in osteomalacia and rickets.
There is no doubt that androgen metabolism also takes place within the skin,with the conversion of testosterone to 5α-dihydrotestosterone by the enzyme 5α-reductase.The skin also contains receptors for other steroid hormones (oestrogens, progestogens, and glucocorticoids) and for vitamin A.

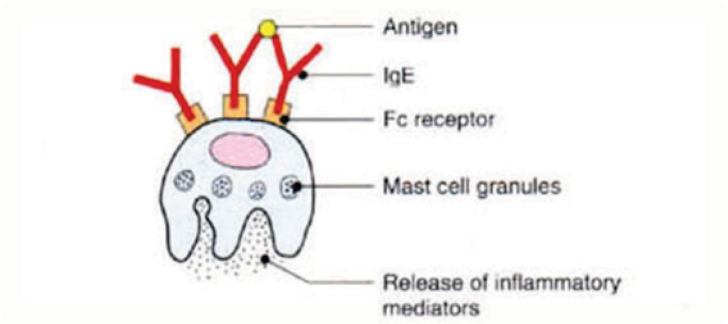
***Social signalling and aesthetic function***
In addition to all above-mentioned mechanistic functions, the skin plays and essential aesthetic role in social interaction and sexual attraction.It is an organ of emotional expression and a site for the discharge of anxiety. The presence of facial blemishes, such as a port-wine stain, or even essentially physiological "abnormalities", such as male balding, excessive hairiness or body ordour, can cause major misery. The skin has great psychological importance at all ages. Caressing favors emotional development, learning and growth of newborn infants. The signs of skin aging, such as wrinkliness of the face or greying of the hair, are often not accepted by some people as a part of life but also serve for them as a cause of anxiety.

***Medical and legal importance of dermatoglyphics***
The fingers and toes, and the palms and soles are interestingly characterizes by remarkable whorled ridge and furrow patterns, known as dermatoglyphics. These characteristic elevated ridge patterns are unique to each individual. The term *dermatoglyphics* is applied to both the configurations of the ridges, and also to the study of fingerprints. The ridge patterns of fingerprints are important both from legal and medical point of view, characteristic dermatoglyphic abnormalities frequently accompany many chromosomalaberrations.

## 4. Hypersensitivity Reactions of the Skin

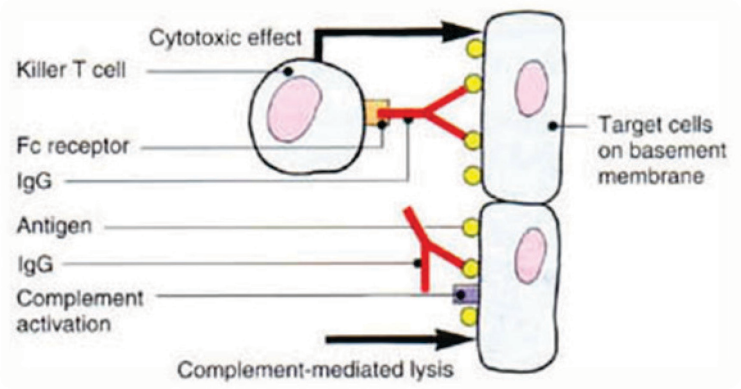
**Hypersensitivity** refers to an inappropriate or exaggerated adaptive immune response that results in tissue damage. There are four main types of hypersensitivity reactions:

**Type 1 (Immediate)**
**IgE** is bound to the surface of **mast cells** via Fc-receptors. Upon binding antigen (pollen, food, etc.), the IgE molecules group together and become **cross-linked** which causes **mast cell degranulation** and release of inflammatory mediators (**histamine, prostaglandins, leukotrienes, etc.**).The response occurs within minutes and can range from skin urticaria to anaphylaxis. There is also a delayed component that is recognized. In addition, other factors, besides IgE, can cause mast cell degranulation.



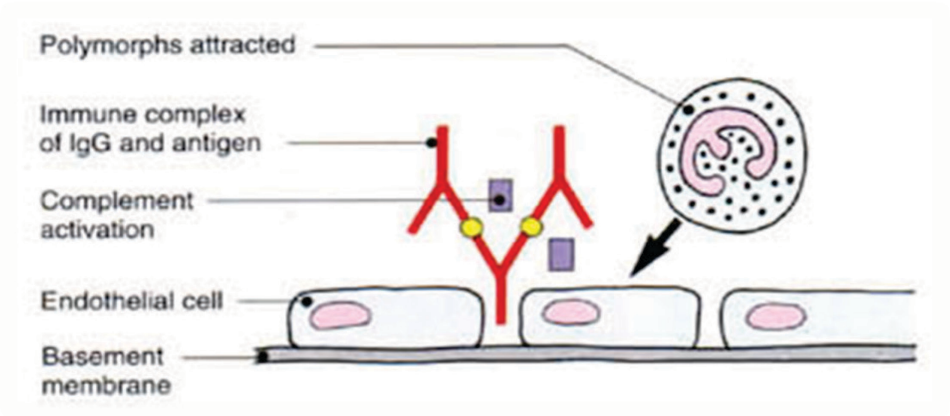

**Type 2 (Antibody-Dependent Cytotoxicity)**

**Antigens** on target skin cells or structures attract**antibodies**. In turn, **killer T cells** and **complement activation** are induced and produce **cytotoxic effects**. This can lead to lysis of keratinocytes and intraepidermal blisters. Other examples of type II reactions are hemolytic anemia, transfusion reactions, and certain autoimmune reactions.



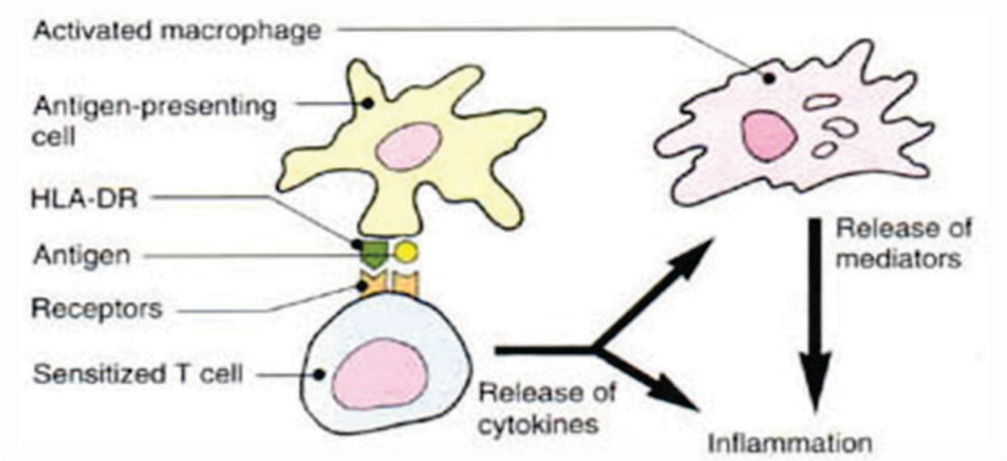

**Type 3 (Immune Complex Disease)**

In the blood, antigen and antibodies form **immune complexes**. These immune complexes are **deposited in the walls of vessels**, especially the small vessels of the skin.**Vascular damage** results as these immune complexes **induce complement, platelet aggregation, and lysosomal enzyme release from polymorphs**. This reaction is seen in systemic lupus erythematosus and dermatomyositis, microbial infections such as infective endocarditis.




**Type 4 (Cell-Mediated or Delayed)**

Antigen is presented to **T-cells** by **antigen presenting cells (APC)**. Released cytokines activate T-cells and amplify the reaction by recruiting more T-cells and **macrophages** to the site of action.**Tissue damage** results which is maximal at 48-72 hours. This reaction is seen in allergic contact dermatitis, and the tuberculin reaction to intradermally administered antigen. Leprosy and tuberculosis are granulomatous variants of the Type IV reaction.



# II. Dermatologic Terminology

An understanding of the basic lesions that occur on the skin is essential to the discipline of dermatology. Lesions are divided into the general categories of **primary** and **secondary**. Primary lesions are those that are directly associated with the disease process and usually appear early in the course of the disease. Those appearing later are called secondary lesions and may be a result of the ongoing disease process and changes to the primary lesions.A morphological classification of dermatological lesions is most helpful to the identification of the diseases present.

## 1. Primary Lesions

– **Macule** - circumscribed area of skin, up to 1.0 cm, with a change from normal skin color, which is neither raised above nor depressed below the surrounding skin. Examples: freckles, flat nevi. **Patch** - a flat, circumscribed, discoloration of skin or mucous membrane greater than 1.0 cm in diameter. Examples: vitiligo, solar lentigines.This term does not include purpura. **Purpura**:larger (greater than 4 mm), circumscribed deposits of blood or blood products in the skin. Example: bruises.Pinpoint(up to 4 mm),circumscribed, non-palpablehemorrhagic macules representingsmall deposits of blood or blood pigments are called **petechiae**.

**Box 2.1. Possible colours and their common causes**:

| Colour | Possible cause |
|---|---|
| **Red** | Hyperemia (erythema), teleangiectases (small dilated vessels), leakage of blood (purpura, petechiae, ecchymosis, suggillation) |
| **Blue** | Cyanosis, hematoma (back eye), dermal melanin, |
| **Brown** | Dermal and epidermal melanin, hemosiderin, |
| **White** | Anemia, vasoconstriction, loss of melanin |
| **Yellow** | Caronenoids, bile, solar elastosis |
| **Gray-black** | Epidermal melanin, heavy metals, tar, dithranol, foreign bodies |

• **Papule**- a discrete solid area of skin that is elevated by palpation above the surrounding skin *and* less than 1 cm in diameter. Variations include acuminate, keratotic, flat-topped, follicular, umbilicated, pedunculated, necrotic and others. Examples: elevated nevi, warts, lichen planus.

• **Plaque** - similar to a papule but greater than 1.0 cm in diameter.Often formed by the confluence or coalescence of papules. Secondary features may include, among others, atrophy, lichenification or hyperkeratosis. Examples: psoriasis, mycosis fungoides.

• **Nodule** - discrete, solid, palpable, round or oval (elipsoidal) lesion of the skin measuring between 1.0 cm and 2.0 cm in diameter (or long axis). Applies to processes involving any or all levels of the skin, and is a general term for any

mass, benign or malignant. Nodule is the deepest primary lesion.Examples: nodular basal cell carcinomas, xanthomas.

- **Vesicle** - a circumscribed fluid-filled lesion less than 1.0 cm in diameter that is usually elevated above the surrounding skin.May be described as solitary, grouped, umbilicated, dyshidrotic, spongiotic, multilocular or unilocular. Examples: herpes simplex, herpes zoster, contact dermatitis.
- **Bulla** - a circumscribed fluid-filled lesion greater than 1.0 cm in diameter that is usually elevated above the surrounding skin. May attain diameters of several cm and are described as tense, or flaccid. Examples: pemphigus vulgaris, bullous pemphigoid, second-degree burns.
- **Pustule** - discrete elevated vesicle or bulla of the skin, usually small, containing purulent exudate composed of inflammatory leukocytes (pus), with or without cellular debris. May be superficial, deep-seated, follicular, grouped, etc. and may arise secondarily from a vesicle. Examples: acne, impetigo.
- **Wheal (urtica, hive)** - an evanescent, round or irregular, often flat-topped elevation of skin with a pale red color, arising from edema in the superficial dermis. May vary from 2-3 mm to 10 or more cm in diameter, with round or arcuate configurations.Should be distinguished from *angioedema*, a massive edema involving the entire dermis and subcutaneous tissues. Examples: hives, insect bites.

## 2. Secondary Lesions

- **Erosion** - a superficial denudation of the skin, usually implying the loss of the epidermis.
- **Ulcer** - loss of skin tissue or substance from the surface downward, leaving an uncovered or denuded wound that is slow to heal.
- **Scale** - a thin flake of epithelium (mostly composed of corneocytes) which is separated from the underlying intact skin proper
- **Crust** - dried surface fluid, often serous in nature, with or without tissue debris.
- **Scale-crust** – a combination of scale (cornified cells, usually parakeratotic ones) and crust (serum that contains blood cells, ether red, white, or both)
- **Fissure** - a vertical splitting or separation of the skin.
- **Scar** - a hard plaque of dense fibrotic tissue covered by a thin epidermis. A mark of injury from any sort of process (physical or pathologic).
- **Excoriation** - a scratch mark, often with denudation of the skin to form a small ulcer.Exposure of the corium by mechanical removal of the epidermis.
- **Lichenification** - a thickening of the skin surface *and* an increase of skin markings, usually seen with chronic coalescence of papular lesions, especially atopic eczema.

## 3. Special Lesions and Conditions of the Skin

- **Atrophy**: thinning of the epidermis leaving an easily wrinkled and/or shiny surface. Atrophy may also apply to dermal and/or subcutaneous tissue, with or without changes in the epidermis.
- **Horn:** projection of keratin
- **Burrows:** small and short or long and tortuous tunnels in the epidermis. Examples: small and short burrows (scabies); long and tortuous burrows (creeping eruptions).
- **Milia (Whiteheads):** whitish papules, 1-2 mm in diameter with no visible opening onto the skin surface. Examples: healed burns, healed bullous disease states, face of newborn babies.
- **Comedones (Blackheads):** plugs of whitish or blackish sebaceous and keratinous material lodged in the pilosebaceous follicle usually seen on the face, the chest and/or back. Example: acne.
- **Cysts:** elevated, circumscribed, encapsulated lesions; in dermis or subcutaneous layer; filled with liquid or semi-solid material. Examples: acne, epidermal inclusion cysts.
- **Tumor**: a term used by some for a "nodule" greater than 1.0 cm in diameter. Applies to processes involving any or all levels of the skin, and is a general term for any mass, benign or malignant. Examples: neurofibromas, large basal cell carcinomas and xanthomas.
- **Telangiectasias:** dilated superficial blood vessels that appear as fine irregular red lines. Example: spider angiomas.
- **Sclerosis:**clinically, a condition of hardness of the skin (morphea).
- **Sinus:** an epithelium-lined channel in the skin that opens on the surface, usually through and infundibular ostium. In contrast to a **fistula** that is open on both ends a sinus is open at one end only.
- **Necrosis:** death of skin that appears black or dark green or purple in color.
- **Wet/Oozing:** the water barrier of the skin has been damaged and there is enough flow of fluid from below to keep the surface of the lesion wet.
- **Maceration:** softened, wettened epidermis

## 4. Descriptive terms necessary for an accurate diagnosis

### *Eruption character*

- **Vegetating**: a lushly growing, proliferating, process, usually with elevated or exophytic features.
- **Eczematous:** This term is used to describe inflammatory conditions of the skin, which appear erythematous and scaly with ill-defined borders. Examples: atopic dermatitis, irritant dermatitis, tinea.
- **Papulosquamous:** This term is used to describe conditions, which manifest themselves as papules or plaques with scales. Examples: psoriasis, lichen planus, pityriasis.

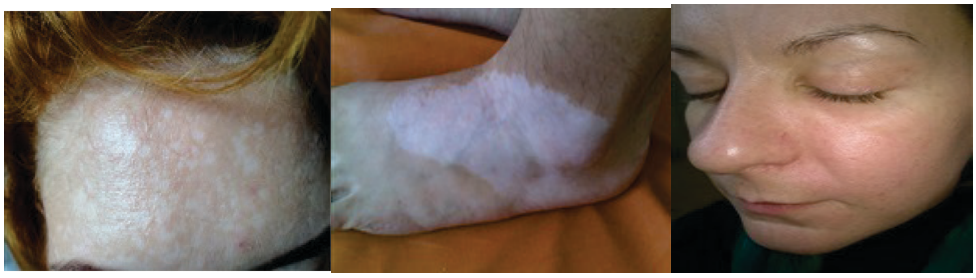
***Eruption surface:*** smooth, rough, warty, papillary, granular, lichenoid, dry, moist, scaly, crusted, erosive, ulcerative, atrophic, shiny, necrotic, elevated.

***Eruption texture:***soft, firm, fragile, tense, elastic, movable.
***Eruption shape:*** round, oval, polygonal, irregular, linear, circinate: arched or rounded border, annular: circular or ring-shaped, discoid, nummular: disk or coin-shaped, serpiginous: winding, twisting (snake-like), iris or cockade (target-like).
***Eruption colour:*** colored, depigmented, hyper- or hypopigmented, pale, anemic
***Eruption distribution:*** localized, widespread, diffuse, centrifugal, linear (following a line), symmetrical, asymmetrical, grouped, isolated from each other, lines of Blaschko (invisible under normal conditions): following embryologic skin lines, reticular (net-like), herpetiform (arranged in clusters, grape-like), zosteriform: following a dermatom, disseminated (randomly distributed).
***Eruption progress:*** rapid, gradual, with or without recurrence.
***Eruption border:*** sharp (well-circumscribed) or vague (blurred).
***Number ofEruptions:*** single or multiple

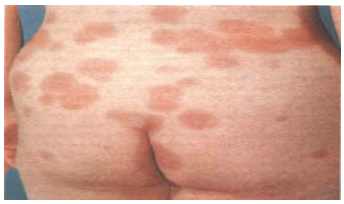
## 5. Characteristics of Individual Lesions

**Macule:**flat, nonpalpable circumscribed area of change in the skin. Macules are < 1-2 cm in size.
**1.** Macules may be the result of **(A)** hyperpigmentation (e.g. brown as in melasma), **(B)** depigmentation (e.g. vitiligo),**(C)** vascular dilation (e.g. erythema).

**A** **B** **C**

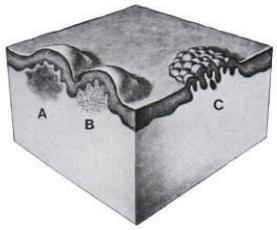


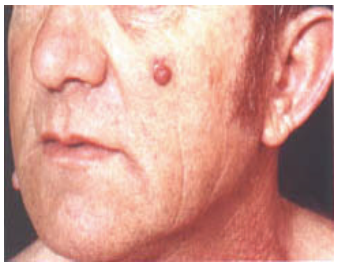
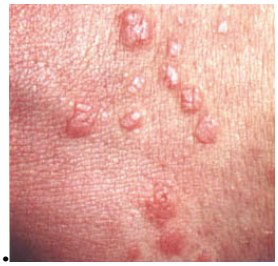
**2.** Multiple well-defined macules of various shapes and sizes. In this case, the macules blanch upon pressure(diascopy) and thus are due to inflammatory vasodilation.



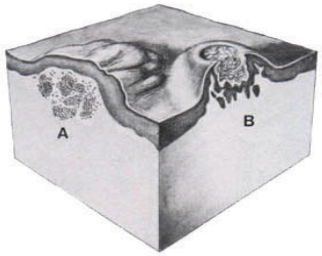
**Papule:** small solid elevation of skin generally < 5 mm in diameter. The majority of the papule elevation projects above the plane of the surrounding skin.
Papules may be flat-topped, as in lichen planus; or dome shaped, as in xanthomas; or spicular, if related to hair follicles.
**1.** Papules may result from **(A)** dermal metabolic deposits, **(B)** localized dermal cellular infiltrates, **(C)** localized hyperplasia of dermal or epidermal cellular elements.

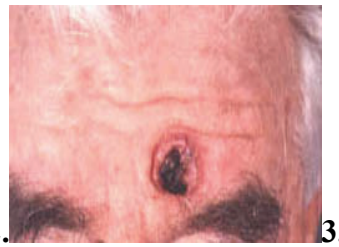
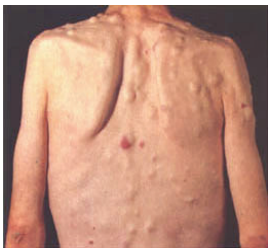
**2.** Two firm dome-shaped papules - dermal melanocytic nevi.
**3.** Multiple well-defined and coalescing papules - lichen planus.

**1.** 

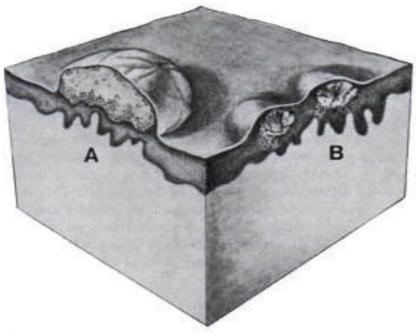
**2.** 
**3.** 

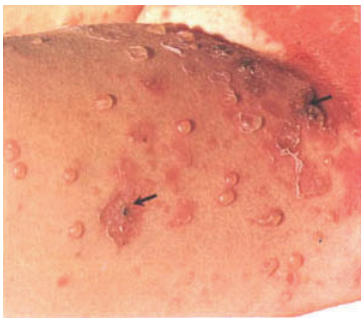
**Nodule:** palpable, solid, round, or ellipsoidal lesion.Its depth of involvement and/or palpability differentiate it from a papule rather than its diameter (although nodules are usually larger than papules: > 5 mm diameter). Nodules can involve any layer of the skin and can be edematous or solid. Based on the anatomical component(s) involved, there are **five types of nodules**: epidermal, epidermal-dermal, dermal, dermal-subdermal, and subcutaneous.
**1.** Nodule can be located in **(A)** the dermis and subcutaneous layer or in **(B)** the epidermis.
**2.** Firm well-defined nodule with a smooth and glistening surface through which dilated capillaries (telangiectasia) can be seen; there is central crusting due to tissue breakdown and thus ulceration - nodular basal cell carcinoma
**3.** Multiple nodules varying in size - melanoma metastases.

**1.** 

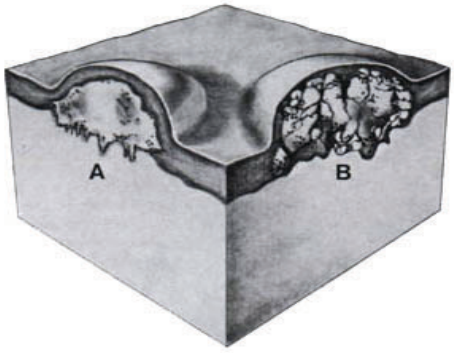
**2.** 
**3.** 

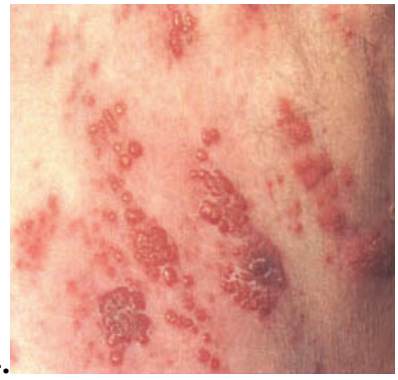
**Vesicle (blister):** circumscribed, elevated lesion that is < 5 mm in diameter containing serous (clear) fluid. A vesicle/bulla is the technical term for blisters. Vesicle walls can be so thin that the contained serum, lymph, blood, or extracellular fluid is easily seen. Fluid can be accumulated within or below the epidermis.
**Bulla:** A vesicle with a diameter > 5 mm.
**1. (A)** subcorneal vesicle - fluid just below stratum corneum, **(B)** spongiotic vesicles - intercellular edema.
**2.** Multiple translucent subcorneal vesicles, extremely fragile leading to crushing (arrows).

1. 

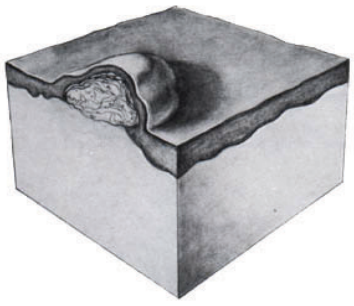

2. 

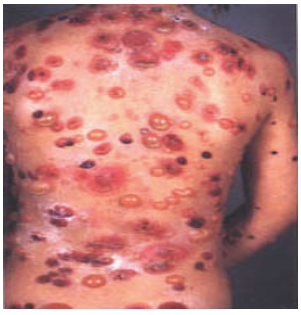
**3. (A)** acantholytic vesicles - cleavage within epidermis due to intercellular attachment loss, **(B)** Balloondegeneration of epidermal cells in certain viral infections leads to vesicles.
**4.**Herpes zoster

3. 

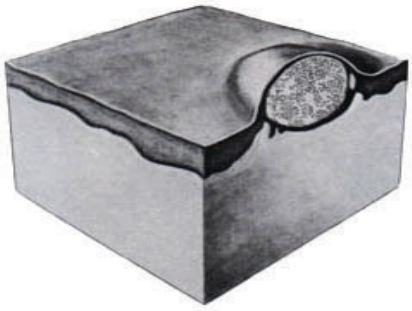
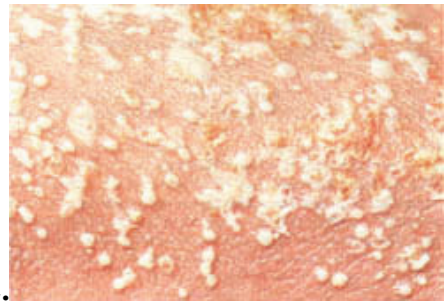

4. 

**5.** Subepidermal vesicles due to changes in dermal-epidermal junction
**6.** Multiple subepidermal vesicles. Vesicles have arisen on normal or erythematous skin. Some vesicles have collapsed and crusted.

5. 

6. 

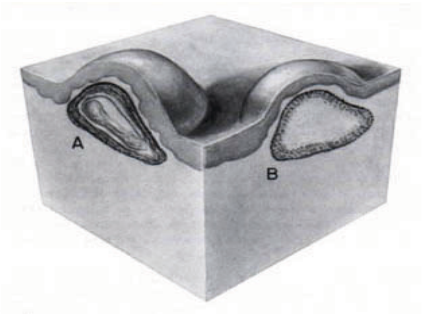
**Pustule:** superficial, elevated lesion that contains pus (pus in a blister). Pustules may vary in size and shape. The color may appear white, yellow, or greenish-yellow depending on the color of the pus. Pus is composed of leukocytes with or without cellular debris. It may also contain bacteria or may be sterile.
**1.** A pustule is basically a papule containing pus.
**2.** Superficial, subcorneal pustules - pustular psoriasis.

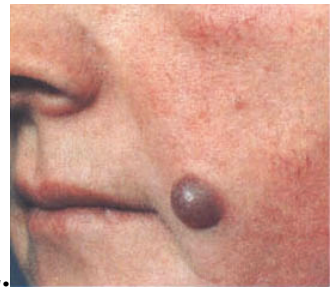
1.  2. 

**Cyst:** an epithelial lined cavity containing liquid or semisolid material (fluid, cells, and cell products). A spherical or oval papule or nodule may be a cyst if, when palpated, is resilient (feels like an eyeball).

**1.** Most common are **(A)** epidermal cysts, lined by squamous epithelium and produce keratinous material. **(B)** Pilar cysts, lined by multilayered epithelium which does not mature through the granular layer.

**2.** Bluish, resilient cyst filled with mucous material - adnexal tumor (cystic hidradenoma).

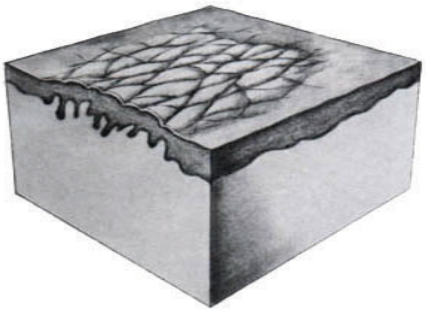
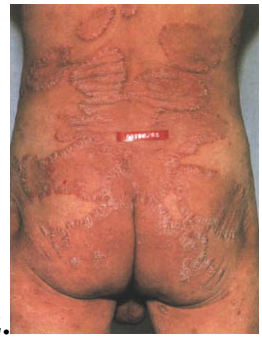
1. 

2. 

**Plaque:** palpable, plateau-like elevation of skin, usually more than 2 cm in diameter and rarely more than 5 mm in height.Often formed by a convergence of papules, as in psoriasis.

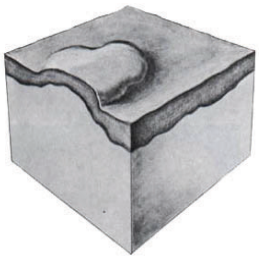
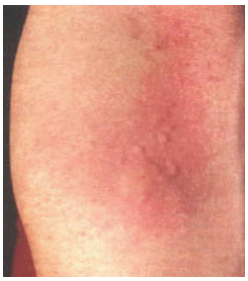
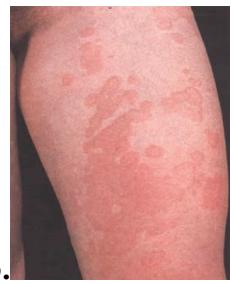
**1.** Plaques occupy a relatively large surface area in comparison with its height above the skin.

**2.** Well-defined, reddish, scaling plaques.

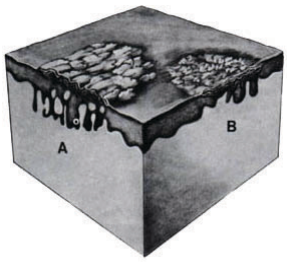
1.  2. 

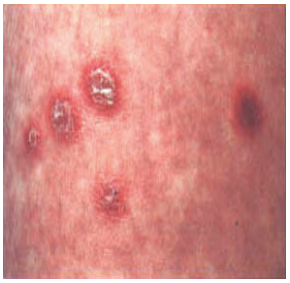
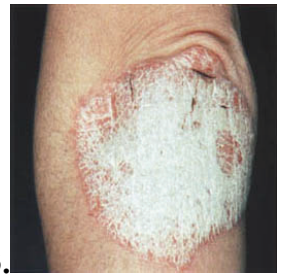
**Wheal:**transitory, compressible papule or plaque of dermal edema.

**1.** The papule or plaque is usually rounded or flat-toped, and evanescent, disappearing within hours. The borders of a wheal are sharp, but not stable and can move from involved to adjacent uninvolved areas over hours.The epidermis is not affected. Wheals can be pale red or white (especially in the center) if edema is sufficient to compress superficial vessels. Wheals are a common allergic reaction.
**2.** A wheal may be large coalescing plaques as in this allergic reaction.
**3.** An eruption of wheals is termed **urticaria** and usually itches.

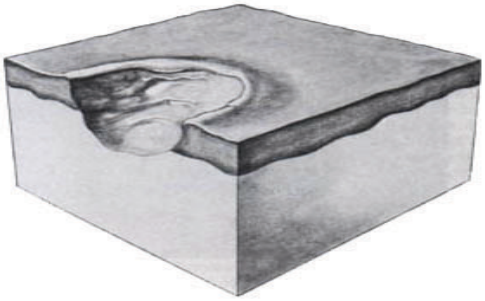
**1.**  **2.**  **3.** 

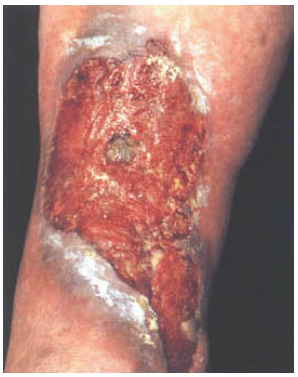
**Scale:** accumulation or abnormal shedding of horny layer keratin (stratum corneum) in perceptible flakes. The change may be primary or secondary. Scales usually indicate inflammatory change and thickening of the epidermis. The may be fine, as in pityriasis; white and silvery, as in psoriasis; or large and fish-like, as in ichtyosis.
**1.(A)** Parakeratotic scale (with retained nuclei) can be seen in psoriasiform epidermal hyperplasia.**(B)** Actinic keratosis is a densely adherent scale with gritty feel due to a localized increase in stratum corneum.
**2.** Typical psoriasis scaling
**3.** Scales may build up to form an asbestos-like layer covering the underlying lesion.

**1.** 

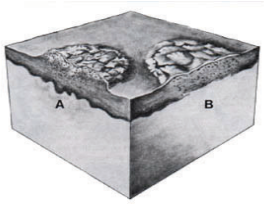
**2.**  **3.** 

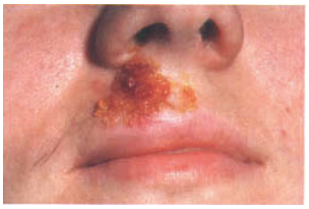
**Ulcer:** circumscribed area of skin loss extending through the epidermis and at least part of the dermis (papillary).
**1.** Basically, it's a "hole in the skin". Ulcers usually result from the impairment of vascular and nutrient supply to the skin.
**2.** Gigantic ulcer, red granulating base with punched out borders.

1. 

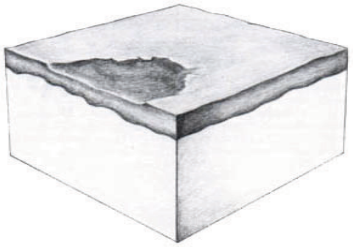
2. 

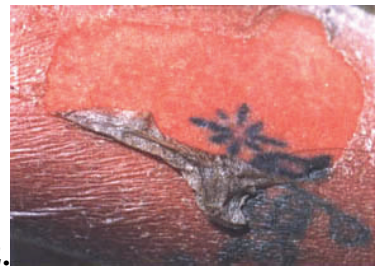
**Crust:** dried serum, blood, or pus on the surface of skin.
**1.** May be thin, delicate, and friable or thick and adherent. Crusts are yellow, if from serum; green or yellow-green if from pus; or brown or dark red if formed from blood. Characteristic of pyogenic infections.
**2.** Crusts that occur as honey-coloured, delicate, glistening particulates are typical of impetigo.

1. 

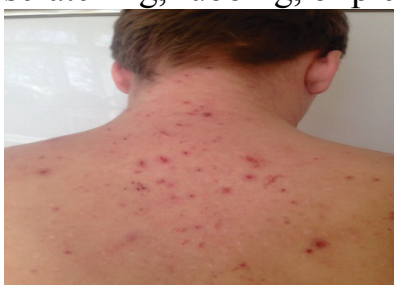

2. 

**Erosion:** moist, circumscribed, usually depressed lesion due to loss of all or part of the epidermis.
**1**. Often results from eruptions of vesicles and bullae. Seen in infection from herpes viruses and in pemphigus.
**2.** Toxic epidermal necrosis causes erosion.

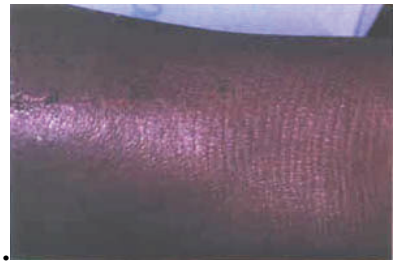
1. 

2. 

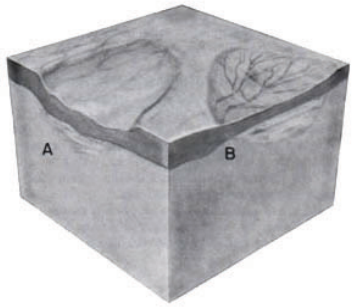
**Excoriation:** linear or punctate superficial excavations of epidermis caused by scratching, rubbing, or picking.

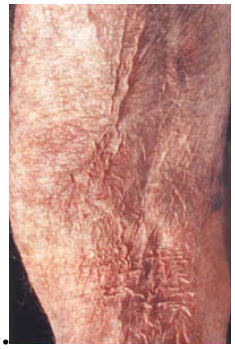


**Lichenification:** chronic thickening of the skin along with increased skin markings.Results from scratching or rubbing.**1.** Note the increased skin markings.

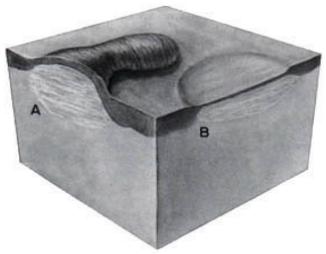
**1.** 

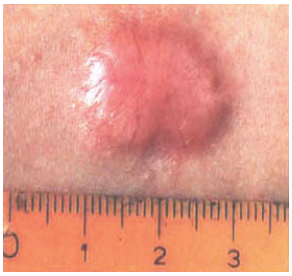
**Atrophy:** paper-thin, wrinkled skin with easily visible vessels. Results from loss of epidermis, dermis or both.Seen in aged, some burns, and long-term use of highly potent topical corticosteroids.
**1. (A)** Dermal atrophy manifests as a depression in the skin. **(B)** Epidermal atrophy manifests as thin almost transparent skin; may not retain normal skin lines.
**2.** Dermal and epidermal atrophy. There is loss of normal skin texture, thinning and wrinkling.

**1.** 


**2.** 

**Scar:** replacement of normal tissue by fibrous connective tissue at the site of injury to the dermis. Scars may be hypertrophic, atrophic, sclerotic or hard due to collagen proliferation. Reflects pattern of healing in the affected area.
**1. (A)** Hypertrophic or **(B)** atrophic scar.**2.** Hypertrophic scar.

**1.** 


**2.** 


## 6. Specific symptoms in dermatology

***Nikolsky's sign*:**a clinical dermatological sign, named after the Russian physician Pyotr Nikolsky (1858-1940). The sign is positive when slight rubbing of the skin results in exfoliation of the outmost layer. Nikolsky's sign is almost always present

in toxic epidermal necrosis (TEN), pemphigus vulgaris, epidermolysis bullosa, staphylococcal scaled-skin syndrome (SSSS). It is useful in differentiation between pemphigus vulgaris (where it is present or positive) and bullous pemphigoid (where it is absent).

***Asboe-Hansen*** sign: also known as "indirect Nikolsky's sign" or "Nikolsky's sign II". It refers to extension of a blister to adjacent unblistered skin when pressure is put on the top of the bulla.

***Koebner phenomenon***: this "isomorfic response means the appearing of specific skin lesions on the site of skin injury. As a rule, lesions have linear distribution. The most common skin disorders with Koenbner phenomenon are psoriasis, lichen nitidus, vitiligo, lichen sclerosus, Kaposi sarcoma, warts. Warts and molluscum contagiosum lesions can be spread in linear patterns by self-scratching ("auto-inoculation").

***Auspitz sign***: used in the psoriasis diagnosis. It is performed by scraping a psoriatic plague with the slides, when the scales exfoliate, pointed bleeding is quickly produced.

**Wickham net**: there are whitish lines visible in the papules of lichen planus, typically the macroscopic appearance of the histologic phenomenon of hypergranulosis.

***Dennie-Morgan fold***: also known as Denni-Morgan line or an infraorbital fold. It is a fold or line in the skin below the lower eyelid caused by edema in atopic dermatitis. The presence of Dennie-Morgan fold is used as a diagnostic marker for allergy.

***"Apple-jelly" symptom***: Diascopic examination of granulomas (tubercules) gives an apple-jelly appearance (yellow-brownish colour of grains). This symptom is positive in cutaneous tuberculosis (lupus vulgaris) and in sarcoidosis of the skin.

# III. DIAGNOSING SKIN DISEASE

## 1. Dermatological Diagnosis

A dermatological diagnosis is a short statement about a disease state or condition. The facts on which a diagnosis of a skin disease is made must always come first and foremost from the patient and there is no substitute for talking to and examining patients. The process of identifying skin diseases consists of (1) taking a history, (2) examining the patient, and (3) performing investigations where necessary.

## 2. Dermatological History –Taking

**Box 3.1.The essentials of dermatological history-taking** are as follows:

**Chief complaint**

- What is the main reason for the patient's visit?
- The duration of the disease?
- What factors provoke the disease? (stress, infection, drugs, food, allergies or others)
- What is the course of the disease (relapses and remissions)?

**Present condition**

- What symptoms (itch, pain, bleeding, numbness or burning sensation, just a cosmetic defect)?
- Intensity of pathologic sensations? What effect do they have on the patient's daily activities and self-image, work, school, sleep, self-confidence, personal relationships?
- Are there systemic symptoms (e.g. high fever, fatigue, joint or/and muscle pain, insomnia)?
- How did the lesion progress? (What factors aggravate the disease? Does it worsen at night?)
- How does the lesion spread? (Is it spreading? Does it occur and disappear rapidly?)

**Past history**

- Past skin disease, significant allergies, general disorders (diabetes, TB)

**Family history/close contacts**

- Any skin disease (some disorders are infectious; others have strong genetic backgrounds)?
- Any allergies or atopic diseases (e.g. hay fever, asthma)?

**Occupation and hobbies**

- Exposure to material in the workplace or at home

**Therapy**

- Medical,systemic and topical, this includes over the counter products and those recommended by non-medical health professionals, e.g. pharmacists, specialist nurses
- Alternative/complementary therapy, exposure to cosmetics and toiletries

– As with any other specialty, the first thing to establish is the presenting complaint. Questions should be asked to define and qualify it, establish whether there are any other linked problems, and to assess its severity.
– There are important genetic aspects to many skin diseases.
– Some skin diseases are infectious or contagious.
– Special attention should be paid to itch which is one of the most specific symptoms of skin diseases.
– Itchy patients can be divided into two groups: those with a rash and those without it; it is important to establish from the beginning whether the itch preceded or followed any skin changes.

**The distribution** of itch may be important, e.g. in dermatitis herpetiformis, itch affects the extensor aspects of the forearms and lower legs and the lower back and scalp, scabies seldom affects the scalp and face in adults.

**The time** when itch is worse may be significant, e.g. itch may be a problem only when the patient is at rest, be worse at night (it characteristically is in scabies), result in loss of sleep (a frequent problem in atopic dermatitis) or be present constantly (as it is when a feature of systemic disease).

**The intensity** of itch may be judged to some extent by the presence of secondary skin lesions caused by scratching (excoriations and bruising)

In should be kept in mind that patients frequently use multiple creams and ointments on their skin - these may have been prescribed by their doctor; already present in the house for other problems or other people; bought “over the counter” at a pharmacy; lent by friends and family; supplied by alternative/complementary practitioners; be part of a cosmetic/toiletryregimen.

## 3. Examination of the Skin

The next step in making a dermatological diagnosis is to examine the patient.

It is considered “the best practice” to examine the whole skin every time.In reality this can be hard on both patient and doctor, especially if the problem is a solitary wart on the thumb. However, as a general rule, and especially with inflammatory dermatoses and conditions with several lesions, it is important to have an overall look at the sites involved.

It is critical to palpate skin lesions as well as to inspect them – not only does this provide useful information but it also indicates to the patient that the doctor, at least, is not repelled or frightened by their rash.

It should be noted that skin diseases are dynamic. Some lesions in any rash will be very early, some very late and some at various intermediate evolutionary stages.

**The fundamental elements** of a good dermatological examination are:

1. Site and/or distribution of the problem
2. Characteristics of individual lesions
3. Examination of "secondary" sites
4. "Special" techniques

## Box 3.2. Key elements in examination of the skin:

**1. Establish the site and distribution of the lesions**

e. g. psoriasis has a predilection for knees, elbows, scalp and lower back; eczema favours the flexures in children; acne occurs predominantly on the face and upper trunk; basal cell carcinomas are more common on the head and neck

2. **Note the characteristics of the individual lesion(s)**

- **The type** (see "Characteristics of Individual Lesions")
- **The size, shape, outline and border** (lesions may be various shapes, e.g. round, oval, annular, linear or irregular; straight edges and angles may suggest external factors; the border is well-defined in psoriasis, but blurred in most patches of eczema)
- **The colour(s)**: red, purple, brown, slate-black, etc.
- **Surface features**: It is helpful to assess whether the surface is smooth or rough, and to distinguish crust (dried serum) from scale (hyperkeratosis); some assessment of scale can be helpful, e.g. " silvery' in psoriasis
- **The texture** - is the lesion superficial and therefore largely epidermal, or is it deep? Use your fingertips on the surface; assess the depth and position in or beneath the skin: lift scale or crust to see what is underneath; try to make the lesion blanch with pressure

**3. Examine secondary sites** (using appropriate secondary techniques – see Box 3.3)

- The nails - in psoriasis, alopecia areata, fungal infections
- The umbilicus – in psoriasis
- The finger-webs and wrists – in scabies
- The toe-webs – in fungal infections
- The mouth – in lichen planus
- The male genitalia – in scabies

## Box 3.3. Examples of secondary examination techniques that can aid diagnosis

- **Scratching, rubbing** or prodding the skin to elicit whealing in: dermographism, mastocytosis - Darier sign
- **Application of ice, warm water, press**ure, etc. to elicit whealing in physical urticaria
- **Scraping a psoriatic plaque** to elicit capillary bleeding – Auspitz sign
- **Easy stripping of the epidermis** in pemphigus and toxic epidermal necrolysis – Nikolsky's sign
- **Blanching** a spider angioma with a fine point
- **Diascopy** (pressure with a glass slide) in cutaneous granulomas, especially cutaneous tuberculosis
- **Wood's light examination** for fluorescence in some fungal infection and for enhancing the visibility of pale patches in tuberous sclerosis

## 4. Special Investigations

Inevitably, history and examination alone will not always provide all the information required. There are some skin disorders in which further investigation is nearly always necessary: either to confirm a diagnosis with important prognostic or therapeutic implications (e.g. blistering disorders), or to seek an underlying associated systemic disorder (e.g.in generalized pruritus). As with all other specialties, dermatology has developed a number of special techniques for advancing the diagnostic information available on an individual patient. Many of these have been used for a long time. Some are much more recent.

### Table 3.1 Investigational Techniques

| **Investigational techniques** | **Potential value** |
|---|---|
| **Blood tests** | For a wide range of underlying systemic abnormalities, for indirect immunofluorescence in immunological disorders and, increasingly, for genetic analysis |
| **Swabs:** | |
| ***bacteriological→*** | *To ascertain nature of infecting organisms, antibiotic sensitivity* |
| ***viral→*** | *To ascertain nature of infecting organism* |
| **Wood's light** | Some disorders/features are easier to see |
| **Skin scrapes or nail clippings** | To obtain material for inspection for fungi, mites, molluscum bodies, giant cells (in herpes virus infections); to set up cultures for fungi |
| **Skin Biopsy:** | |
| ***light microscopy→*** | Pathological interpretation, including special stains and immunohistochemistry as necessary |
| ***immunofluorescence→*** | *Bullous disorders; cutaneous and systemic lupus erythematosus; vasculitis* |
| ***electron microscopy→*** | *Especially useful in congenital and acquired blistering diseases* |
| ***culture→*** | *The organisms causing TB, leishmaniasis, and some rare organisms are more easily, or can only be cultured from skin biopsies* |
| ***in-situ hibrisization→*** | *Sybtyping human papilloma virus* |
| **Patch tests** | For evidence of contact allergy |
| **Dermatoscopy** | Useful in distinguishing benign from malignant skin lesions |

## 4.1. Scrapings/Cippings/Smear Preparations

Material from the skin, hair or mails can be examined directly under the microscope and/or sent for culture. This is particularly useful in suspected fungal infection, or in a search for scabies mites.

### *Diagnosis of fungal infections*

Potassium hydroxide (KOH) is used for observation and detection of fungi and mites. The scales are placed on a microscopic slide with some drops of 20% KOH solution and covered with a coverslip. The slide is heated on a hot plate at 70$^{o}$C to 80$^{o}$C for 5-10 minutes. The horny cell layers are hydrolyzed and the fungal elements can be seen as mycelial strands crossing cell boundaries. Scabies mites,

egg, egg cases or immature forms are also easily seen under low power. Nail clippings can also be treated this way.
Microscopy of hair may also provide information about fungal infections, may reveal structural hair shaft abnormalities in certain genetic disorders, and can be useful in distinguishing some causes of excessive hair loss.

***Cytologial diagnosis (Tzank test)***
Scrape/smear preparations are also uses as a diagnostic aid for the cytodiagnosis of suspected viral blisters and pemphigus, using a "Tzank preparation".
**Herpes infection diagnosis**is conducted by applying a slide glass to the bottom of erosion or the content of a vesicle and staining the adherent cellular components in Giemsa for observation under a light microscope. Ballooning keratinocytes produced by viral infection are observed. They look like multinuclear giant cells ("Tzank cells").
**Pemphigus diagnosis** is conducted by applying a slide glass to the bottom of a blister and staining the adherent cellular components in Giemsa for observation under a light microscope. Acantolytic cells called Tsanck cells are observed in pemphigus. The term "acantolytic cell" refers to a epithelial cell that has undergone dyshesion (i.e. separation from another epithelia cell) by dissolution of intercellular bridges and has consequently become round.

## 4.2. Wood's Light

A Wood's light is a nickel oxide-filtered ultraviolet light source emitting ultraviolet light in the wavelength of 360 nanometers which is used to highlight three features of skin disease (see Table 4.2):
1) Certain organisms which cause scalp fungal infection (ringworm) produce green fluorescence (useful in initial diagnosis and helpful in assessing therapy).
2) The organism responsible for erythrasma fluoresces coral-pink.
3) Some pigmentary disorders are more clearly visible – particularly the pale patches of tuberous sclerosis and café-au-lait marks of neurofibromatosis.
4) Wood's light can also be used to induce fluorescence I the urine in some of the porphyrias.

**Table 3.2 Wood's Light Examination in Different Skin Disorders**

| **Disease** | **Coloration** |
|---|---|
| ***Fungal infection*** | |
| Tinea capitis associated with Microsporum species and favus | Green |
| Pityriasis versicolor | Brownish-yellow |
| ***Bacterial infection*** | |
| Erythrasma | Coral-pink |
| ***Pigmentary disorders*** | |
| Vitiligo<br>Tuberous sclerosis<br>Café-au-late marks | Bright white or<br>more clearly visible |

## 4.3. Dermatoscopy

Dermatoscopy (also known as dermoscopy or epiluminiscence microscopy) is the examination of skin lesions with a dermatoscope. This traditionally consists of a magnifier (typically x10), a non-polarized light source, a transparent plate and a liquid medium between the instrument and the skin, and allows inspection of skin lesions unobserved by skin surface reflections. This instrument is useful in distinguishing benign from malignant (cancerous) lesions, especially in the diagnosis of melanoma.

## 4.4. Direct Immunofluorescence (DIF)

DIFinvolves the overlay of fluorescein-conjugated antibodies (IgG, IgM, IgA),complement (C3) and fibrinogen onto frozen sections of tissue obtained from patients. Biopsy specimens for direct immunofluorescence in immunobullous diseases should be taken from perilesional normal-appearing skin within a few millimeters from the edge of the blister. However, when a biopsy specimen is needed for diagnosis of connective tissue disease or vasculitis, a lesional biopsy is optimal.

**Table 3.3.Direct Immunofluorescence in Some Inflammatory Skin Disorders**

| Skin disease | Deposition | Site of deposition |
|---|---|---|
| **Pemphigus vulgaris** | IgG, complement C3 | Intercellular (around keratinocytes of stratum spinosum) |
| **Bullous pemphigoid** | IgG, complement C3 | Linear in the epidermal basement membrane |
| **Dermatitis herpetiformis** | IgA | Granular deposition on the papillar layer in derma |
| **Lupus erythematosus** | IgG, IgM | Linear on the basement membrane and around hair follicles |
| **Vasculitis** | IgM, IgG, C3, fibrinogen | Strong dermal blood vessels |

## 4.5. Indirect Immunofluorescence

Indirect immunofluorescence studies involve the detection of circulating autoantibodies in the patient's serum which target specific antigens in the patient's skin or mucosa. The technique for indirect immunofluorescence is helpful in immunobullous diseases. It includes incubation of patient's serum which contains the antibodies with frozen sections of epithelial substrate. The substrate is usually a monkey esophagus, but a pig esophagus also may be. The rat bladder is used to rule out paraneoplastic pemphigus. After washing, the fluorescence-labeled animal anti-IgG-conjugate binds to the patient's circulating IgG, which is already bound to the target antigen on the epithelium surface.

**Note: the serology tests are also used in dermatology for the detection of antibodies to syphilis and HIV.**

## 4.6. Skin Biopsy

Biopsy of skin lesions is useful to establish or confirm a clinical diagnosis. In some cases, such as skin cancers, bullous disorders and infections, such as tuberculosis and leprosy, it is critical to have confirmation of a clinical diagnosis.In others biopsy is necessary because clinical information alone has not provided all the answers. In case of a biopsy a piece tissue is removed surgically for histologic examination and sometimes for other tests (e.g. culture for organisms).

***Indications for biopsy***:
- You cannot make a diagnosis;
- The disorder does not respond to treatment;
- The disorder is unusual or severe; or
- You are just not sure.

***Biopsy technique selection***
Six major methods are employed to biopsy skin: curettage, snip or scissors biopsy, shave biopsy, punch biopsy and excision *in toto.*
**Curettage** is frequently used to remove clinically benign lesions; a curette 3-5 mm in diameter is held like a pencil and drawn with pressure under the lesion (if epidermal) or through the lesion (e.g. presumed basal cell carcinoma).
**Snip or scissors biopsy** is an efficient technique for assessing pedunculated lesions as well as removing benign growth (e.g. acrochordons, filiform warts).
**Shave biopsy** usually provides a specimen consisting of epidermis, papillary dermis and, sometimes, reticular dermis (particularly in elevated lesions). It is a popular biopsy technique for ”planing” popular, clinically benign lesions (e.g. irritated or unwanted compound and dermal melanocytic nevi, fibrous papules of the nose) where histological confirmation is desired, also a useful procedure for diagnosing superficial carcinomas, lentigo maligna.
**Punch biopsy** supplies a cylindrical to conically shaped specimen consisting of epidermis, dermis and, sometimes, subcutaneous fat. The volume of tissue sample correlates with the size of the punch biopsy instrument. In general, its diameter varies from 2 to 6 mm and the wider the diameter, the greater the likelihood of obtaining subcutaneous fat. Punch biopsy is much quicker than incisional/excisional biopsy, but produces small samples and is only appropriate for diagnosing biopsies or removing tiny lesions.
**Incisional biopsy** removes a wedge of tissue from the center or edge of a lesion and is the best option for obtaining deep subcutaneous fat or fascia for histological examination. It is also used to sample a significant portion of large-sized tumours.
**Excision***in toto* removes the entire lesion and includes epidermis, dermis and subcutaneous fat. For these reasons, it is often the biopsy of choice for a presumed invasive cutaneous melanoma.
***Site preparation and anesthesia***

It is important to choose an appropriate area from which to take the sample. The skin lesion(s) should be fully formed. Late lesions should be avoided. In some situations (e.g. dermatitis herpetiformis and bullous pemphigoid), it is important to sample early lesions because the classic histology may be altered by the passage of time.
Marking the site, cleansing the skin, and draping are important prior to performing local anesthesia. Local anesthesia is adequate for all skin biopsies. The agent generally used is lidocaine, either at a 1% or 2% concentration. Epinephrine may be added to the lidocaine in order to reduce bleeding and prolong anesthesia, but it is avoided in patients who have a proclivity for cardiac arrhythmias. Topical agents include eutectic mixture of local anesthetics (e.g. EMLA® with lidocaine and prilocaine), tetracaine, liposome-encapsulated tetracaine, and liposome-encapsulated lidocaine.

***Specimen handling***
Transportation of the biopsy specimen to the laboratory differs according to the processing and type of examination required. Most specimens are placed in 10% formalin, but, occasionally, special carrier media are necessary, e.g. Michel's medium for direct immunofluorescence. Fresh tissue specimens for direct immunofluorescence, immunoperoxodase, culture for bacteria, mycobacteria or fungi are sent on saline-moistened gauze and either promptly delivered to the laboratory or packed in ice; the laboratory must be on reasonable proximity and have the capability of processing the tissue immediately. For culture for viruses viral transport medium is necessary.

***Hemostasis***
All methods of biopsy require attention to hemostasis of the wound bed. For small-diameter, superficial wounds, compression alone may be used. Styptics such as aluminum chloride hexanydrate (Drysol$^{TM}$, Xerac AC$^{TM}$) and ferric subsulfate (Monsel's solution) are frequently used. Punch biopsy sites are usually closed primarily and the suturing itself creates sufficient hemostasis. Wounds created during incisional biopsy or excision *in toto* may require electrocoagulation for hemostasis before closure.

## 4.7.Patch Test

The patch test is the most frequent test for detection of specific substance causing allergic inflammation of the skin. A patch test relies on the principles of a ***type IV hypersensitivity reaction***.
The general rules for patch testing:
– Complete healing or remission need to be achieved before patch testing
– Avoid patch testing on markedly tanned persons
– Do not test pregnant women
– The preferred site is the upper back
– Clip hair one or two days before testing

– Patients should be informed as to the aim of the test; about avoidance of showers, wetting the test site, irradiation and excessive exercise, and about symptoms such as itch and discomfort.

The standard patch test technique involves application of the test allergen strips to the skin under occlusion for 48 hours. Interpretation of results is performed at the $3^{d}$-$4^{th}$days and and the $7^{th}$ day after occlusion (i.e. 1, 2 and 5 days after the removal of the patch test strips).

**Table 3.4.Scoring of Patch Test Reactions**

| Score | Interpretation |
|---|---|
| - | Negative reaction |
| ?+ | Doubtful reaction: faint erythema only |
| + | Weak (non-vesicular reaction; erythema, slight infiltration |
| ++ | Strong (edematous or vesicular) reaction; erythema, infiltration, vesicles |
| +++ | Extreme (bullous or ulcerative) |
| IR | Irritant reaction of different types |
| NT | Not tested |

## 4.8. Other SkinTests

**Stripping test** is a variant of patch testing consisting of "stripping" the stratum corneum before applying the allergen in the usual way to suppress the skin barrier.

**Open test**. Skin allergens are dropped onto the volar forearm and allowed to spread freely. No occlusion is used.

**Semi-open test** is a variant of the open test covered by a non-occlusive tape. It is thus "half-way" between open testing and conventional patch testing.

**Repeated open application test**. Allergens are applied twice daily for 7 days to the outer aspect on the upper arm, antecubital fossa or back skin (scapular area). A positive result (eczematous dermatitis) may appear on the 2-4 days but it is recommended to extend the application beyond 7 days so as not to miss late-appearingreaction.

**Prick test** is a test method for detecting immunoglobulin E (IgE)-mediated allergy. Drops of allergen solution are applied to the volar aspect of the forearm or to the upper part of the back. When drops of allergen solutions are applied to the skin, they are pierced with a special lancet for penetration of allergens into epidermis. No bleeding may occur. Conventional time reading is 15-20 min. Prick testing of allergen needs the concomitant use of controls, positive and negative. Histamine chlorhydrate solution and codeine phosphate solution (9%) are used as positive controls. Saline and/or vehicle of the allergens is used as a negative control.

**Scratch test** is a common method for detecting immediate allergy. It is still used when only non-standardized allergens are available. A scratch of approximately 5 mm long is made with a blood lancet and bleeding is avoided. The back and arms are the preferred test sites. Scratch testing of allergens needs the concomitant use of controls, positive and negative.

# IV. BASICS OF MEDICAL THERAPY IN DERMATOLOGY

Medical treatment in dermatology consists of: topical therapy, systemic therapy, phototherapy and surgical procedures.

## 1. Topical Therapy

The advantage of direct delivery and reduced systemic toxicity make topical treatment quite attractive.All topical agents are "held" in a base of some kind, the so-called "vehicle", which allows the patient to apply the material to the skin surface.

### 1.1. Vehicles

**Cream** – a semi-solid emulsion of oil-in-water; contains a preservative to prevent overgrowth of microorganisms. It is stabilized by an emulsifier and contains mostly water, so mostly evaporates. As the proportion of oil increases, the preparation approaches the consistency of ointment, which is the most lubricating vehicle. Creams are not greasy and easy to remove. Effects of creams are cooling, vasoconstrictive, anti-inflammatory. They are often used for dry skin lesions. Creams are more superficial comparing with ointments.
**Gel** – a semi-solid transparent non-greasy emulsion. Gels are aqueous preparations that liquefy on contact with the skin and leave a uniform film on drying. They are well-tolerated in hair-bearing regions.
**Lotion** – a liquid vehicle, aqueous or alcohol based (in the latter case it is used especially on the scalp to avoid matting of the hair), which may contain a salt solution. Lotions evaporate and cool the skin. They are useful for inflamed and exudative conditions.
**Ointment** –is a topical vehicle of semi-solid grease or oil with little or no water. Ointments are occlusive and allow for high transcutaneous penetration of the active drug. They are stable for a long period of time. An ointment is the best therapeutic option in the treatment of thick infiltrates of the skin (plaques), because they can penetrate to the deep layers of the skin. Ointments rehydrate, moisturize, but because of the greasiness they are difficult to remove.
**Paste** – an ointment with a high proportion of powder which gives a stiff consistency. Pastes can be applied to well-demarcated lesions. Due to its ointment base, they are difficult to remove.
**Powders** promote drying and are especially useful in intertriginous areas but in the wet areas powder can form clumps. They are used in subacute processes without weeping.
**Aerosols and sprays** act in a manner similar to lotions and gels. Active ingredients are incorporated into aqueous phase. A convenient delivery system usually allows for easy dispersion over the skin surface. Aerosols are also particularly useful on the erosive and ulserative lesions.

**Solutions** possess anti-inflammatory and cooling effects. The main indication for solutions in dermatology is wet dressings in acute exudative skin surface (eczema, pyoderma).

### Box 4.1.The vehicle is prescribed according to the stage of the inflammation process

**Acute inflammation** (weeping, bright erythema, edema, erosion) → sprays, wet-drying bandages, solutions
**Acute inflammation without weeping** (hyperemia, swelling) → creams, lipocreams, pastes, aerosols
**Subacute inflammation** (light swelling and hyperemia, mild itching) → creams, lipocreams, pastes, ointments
**Chronic inflammation** (lichenification, infiltration) → hot compresses (occlusion), ointment, keratolytic and keratoplastic ointments
**Hyperkeratosis** (palms and solves) → keratolytic ointment under occlusion

In general terms, the greasier a base is the more occlusive it is. This also generally implies a greater degree of emolliency or moisturizer effect, as it prevents water loss to a greater degree. On the other hand, a lighter cream is much easier to use and is much more cosmetically acceptable to most patients.
Some of the more modern oily creams aim to achieve a balance between these two extremes, by providing a higher degree of occlusion and emolliency with a lower and more acceptable degree of "greasiness". Some agents designed purely to be emollients contain additional elements (such as urea, allantoin, or aloe vera) which are claimed to increase the moisturizing effects

## 1.2. Quantities Required

A useful guide is the fingertip unit (FTU) which equals ½ g. One FTU is the amount of topical agent that can be applied to the terminal phalanx of the index finger.The whole body requires 20-30 g of ointment per single dose.

### Table 4.1 Ointment per Single Dose In an Adult

| Body part | Quantity |
|---|---|
| Face or neck | 1g |
| Trunk (each side) | 3g |
| Arm | 1 ½ g |
| Hand | ½ g |
| Leg | 3 g |
| Foot | 1 g |

## Table 4.2 Overview of Topical Medications

| Drug | Pharmacology | Indications |
|---|---|---|
| **Antibiotics** | Resistance and sensitization are potential problems. Bacitracin, chlortetracycline, gramicidin, mupirocin, neomycin, polymixin, sodium fusidate. Metronidazole is used for rosacea. | Acne, folliculitis, impetigo, infected eczema, rosacea. |
| **Antifungals** | Polyenes, imidazoles (more than 20), allylamines,hydroxypyridones,morpholines, benzylamin | Fungal infections of the skin, candidiasis. |
| **Antiseptics** | Chlorhexidine, iodine compounds, potassium permanganate, silver nitrate. | Skin sepsis, leg ulcers. |
| **Antivirals** | Acyclovir, penciclovir, docosanol | Herpes simplex and zoster. |
| **Coal tar** | Presumed anti-inflammatory and anti-proliferative effects. | Eczema, psoriasis. |
| **Corticosteroids** | Anti-inflammatory, anti-proliferative, vasoconstrictive effects; different strengths available. | Eczema, discoid lupus erythematosus, lichen planus, lichen sclerosus, mycosis fungoides, photodermatoses, pityriasis rosea, psoriasis. |
| **Dithranol** | Anti-proliferative effect | Psoriasis. |
| **Topical immunomodulators** | Modulate immune function: tacrolimus and pimecrolimus | Atopic dermatitis |
| **Retinoids** | Chemically related to vitamin A: tretinoin adapalen, isotretinoin, tazaroten | Moderate and mild forms of acne, actinic keratosis, plan warts, photoaging |
| **Vitamin D analogues** | Inhibit keratinocyte proliferation and promote differentiation:calcipotriol, tacalcitol. | Psoriasis |
| **Keratolytics** | Salicylic acid, benzoyl peroxide | Acne, scaly eczemas |
| **Diphencyprone** | Induces allergic contact dermatitis | |
| **Parasiticidals** | Malathion, permethrin, carbaryl for lice. Benzyl benzoate, lindane, malathion, permethrin for scabies. | Lice, scabies |

## 1.3.Topical Corticosteroids

Topical corticosteroids are undoubtedly the mainstay of the treatment of all the eczema/dermatitis group of conditions and of many other inflammatory dermatoses (e.g. lichen planus and lupus erythematosus). They also have a valuable role in psoriasis, especially on certain sites. However, topical corticosteroids need to be handled with care. They have the potential to cause significant skin atrophy if they are applied to the same area of skin repeatedly over many weeks or months. They reduce the skin's resistance to superficial infections. They can inhibit the pituitary-

adrenal axis if sufficient quantities are applied to lead to significant systemic absorption.

It is important to appreciate that topical corticosteroids are by no means “all the same”:some are much stronger than others (Table 4.3). Furthermore, several factors increase the potential for atrophogenicity and absorption:

The base – ointments>creams>gels>lotions.
The site of application – the face and flexures are much more vulnerable.
The size of the patient – children have a higher surface-area-to body-mass ratio and are more susceptible to absorption of steroids.
The use of occlusive dressings over the steroids (especially polythene).

**Table 4.3 Steroid Potency**

| **Potency** | **Examples** |
|---|---|
| Mild | Hydrocortisone |
| Moderately potent | Alcometasone dipropionate<br>Hydrocortisone with urea |
| Potent | Betametasone valerate<br>Fluocinolone acetonide<br>Fluocinonide<br>Hydrocortisone butyrate |
| Very potent | Clobetasol propionate |

The most appropriate topical steroid for a givensituation should be determined by the type and severity of the condition being treated, the sites affected, and the age of the patient. In general, a severe dermatosis should be treated with a potent steroid, and a mild condition with a weak steroid. In the case of a chronic dermatosis subject to periodic exacerbations a mild to moderate potency steroid can be used when the condition is quiescent, and a potent preparation when it worsens.
There are regional variations in the absorption of topical steroids through the skin and their potential for local adverse effects. These variations are determined by the thickness of the stratum corneum, occlusion, for example in the flexures where skin surfaces are in apposition, and the vascularity of the area. Most facial dermatoses should only be treated with mild topical steroids, although a few conditions such as discoid lupus erythematosus will require potent preparations. Skin diseases affecting the axillae, groins and submammary areas should also be treated with mild topical steroids. Conversely, dermatoses of the palms and soles, where the stratum corneum is extremely thick, require potent steroids, and a greater benefit is often obtained if polythene occlusion is used to enhance penetration.
There is a greater risk of adverse systemic effects from the use of topical steroids in children because of the high ratio of skin surface area to body volume, particularly in infants. For this reason mild topical steroids should be used in small children. The skin of the elderly is thin and potent steroids will amplify this change

– their use over long periods of time should therefore be avoided or carefully supervised.

**Side effects of steroid topical application**

***Skin atrophy.*** Repeated use of topical steroids in the same area can cause thinning of the epidermis and changes in the connective tissue of the dermis. The skin becomes lax, wrinkled, and shiny with visible teleangiectasias, hypopigmentation, and prominence of underlying veins. In most cases the atrophy is reversible once topical steroid use is stopped, but it may take month for the skin to "thicken" back up.

***Tachyphylaxis***. Tachyphylaxis is the tolerance which the skin develops to the vasoconstrictive action of topical steroids. After repeated use of topical steroids the capillaries of the skin do not constrict as well requiring higher doses or more frequent application of the steroid. The ability of the blood vessels to constrict returns 4 days after stopping therapy.

***Steroid rosacea***. This is a side effect commonly observed in fair-skinned people who already have rosacea. A typical example occurs when a person uses a very mild steroid on the face to counteract the facial flashing and teleangiectasia. This gives pleasing results, but tolerance develops causing the person to use a higher strength steroid. At this point any attempt to cut down on the steroid application or stop altogether causes intense facial redness and pustules.

***Striae – stretch marks.*** Repeated use of topical steroids in arrears where skin touches skin such as the groin and armpits can result in striae,or stretch marks. Stretch marks from topical steroids are permanent and irreversible. It is recommended to progressively decrease the steroid potency until topical steroid therapy in these areas can be terminated.

***Alteration of infection***. Because topical steroids change the way the immune system functions, they can inhibit the skin's ability to fight off bacterial or fungal infections. A typical example of this is seen when someone applies a topical steroid to an itchy groin rush. If this is a fungal infection, the rash gets redder, itchier and spreads more extensively than a typical fungal infection. The resulting rash is a bizarre pattern of widespread inflammation with pustules called tinea incognito.

***Topical steroid allergy.***Some people may be allergic to a component of a topical steroid base or vehicle. People who have chronic skin conditions and use multiple prescriptions or over the counter topical steroids are at higher risk of developing allergies to topical steroids.

***Systemic side effects***. As long as the doses of steroids are appropriate, systemic side effects are rare. However, when strong steroids are applied on a large area for a long period or when they are used in occlusive therapy, side effects similar to those caused by steroid systemic administration may be produced (e.g. iatrogenic Cushing's syndrome).

## 1.4. Topical Retinoids

There is now consensus that topical retinoids should be used as the first-line therapy, alone or in combination, for mild-to-moderate inflammatory acne and are also preferred agents for maintenance therapy. Their effectiveness is well documented, as they target the abnormal follicular epithelial hyperproliferation, reduce follicular plugging, microcomedones and both non-inflammatory and inflammatory acne lesions.
Tretinoin, adapalen, isotretinoin, taxaroten are effective comedolytic agents. Topical tretinoin is also effective in actinic keratosis, and plane warts.
Isotretinoin and tazaroten were found to improve photoaging skin changes. Epidermal melasma, actinic lentigines, superficial post-inflammatory hyperpigmentation also respond to topical tretinoin, either alone or in combination with hydroquinolone and hydrocortisone.

### Table 4.4Topical Retinoids

| Substance | Vehicles | Indication |
|---|---|---|
| **Adapalen** | 0,1% gel, solution, cream | Mild/moderate acne |
| **Alitretinoin** | 0,1% gel | AIDS-related Kaposi's sarcoma |
| **Bexaroten** | 0,1% gel | Cutaneous T-cell lymphoma |
| **Isotretinoin** | 0,05% gel; 0,05%, 0,1% cream | Mild/moderate acne, photoaging |
| **Tazaroten** | 0,05%, 0,01% gel | Psoriasis, mild/moderate acne |
| **Tretinoin** | 0,025%, 0,1%,0,05%, 0,1%, 0,4% cream 0,025% gel, 0,05%, 0,1%, 0,2% solution, 0,1% ointment | Mild/moderate acne, photoaging Cosmetic indications |
| **Tretinoin** | 0,025% cream | Inflammatory rosacea |

## 1.5. Topical Antifungal Agents

There is a wide variety of topical antifungal agents but there is no truly effective topical agent for onychomycosis, although nail vanishes (ciclopirox 8% and amorolfin) are now available for treatment of onychomycosis. The spectrum of action of topical anifungal agents is shown in Table 4.5.

### Table 4.5. Topical Antifungal Agents and Their Spectrum of Action

| Agent | Spectrum of action | | |
|---|---|---|---|
| | **Dermatophytes** | **Yeasts** | **Molds** |
| **Polyenes** | | | |
| - Amphotericin B | + | | |
| - Nystatin | + | | |
| - Natamycin | + | + | + |
| **Imidazole (more than 20)** | + | + | + |
| **Allylamines** | | | |
| - Naftifin | + | | |
| - Terbinafine | + | | |
| **Hydroxypyrudones** | | | |

| | | | |
|---|---|---|---|
| - Ciclopirox | + | + | + |
| **Morpholines** | | | |
| - Amorolfin | + | | |
| **Benzylamine** | | | |
| - Butenafin | + | | |
| **Others** | | | |
| - Tolnaftat | + | | |
| - Clioquinol | + | | |
| - Undecylenic acid | + | | |
| - Iodoquinol | + | | |

## 1.6. Topical Immunomodulators

Two agents that modulate immune function after topical application are tacrolimus and pimecrolimus. They have been primarily introduced for the treatment of atopic dermatitis. Both exert their effect predominantly by calcineurin inhibition, which alters T-cell reactivity. They have both been shown to be effective in atopic dermatitis, and successful use in other disorders is being reported. They have the obvious advantage of not being corticosteroids and therefore avoiding steroid side-effects, notably cutaneous atrophy.

## 1.7. Other Topical Dermatological Preparations

***Salicylic acid***

Salicylic acid "softens" keratin and helps to remove scale from psoriasis and from very scaly disorders, especially in the scalp. It is therefore often added to mixtures of tar and steroids. Salicylic acid in higher concentrations is also used to treat viral warts.

***Tar and dithranol***

Tar is soothing to itchy, inflamed skin. It is also a valuable adjunct in the management of psoriasis, where it seems to augment the effects of ultraviolet radiation. Dithranol is a strange material, originally isolated from Goa powder, which can return psoriatic skin to normal. It can cause quite nasty burns, however, and it also oxidizes to a brownish purple dye. It is used in creams and ointments and in a complicated, stiff paste known as Lassar's paste.

***Vitamin D analogues***

Vitamin D analogies are relatively new, but have quickly found and important place in the management of plaque psoriasis. Reports of improvement have also been recorded on other hyperkeratotic disorders such as pityriasis rubra pilaris, ichthyosis, porokeratosis and epidermal nevi.

***Diphencyprone***

There are good studies that have shown that the application of agents that induce allergic contact dermatitis can encourage regrowth in alopecia aerated, although the percentage of those who derive persisting benefit is small. Diphencypron

appears to have replaced some of the earlier alternatives because it is safer (not oncogenic).

## 2. Systemic Therapy

Systemic therapy is reserved for more serious condition and infections (see Box 4.1).

**Box 4.1 Systemic therapy**

| Group | Drug | Indications |
|---|---|---|
| **Antiandrogens** | Cyproterone | Acne (only in females) |
| **Antibiotics** | Various | Acne, rosacea, skin sepsis, bacterial infections |
| **Antifungals** | Griseofulvin<br>Ketoconazole<br>Itraconazole<br>Terbinafine | Fungal Infection<br>Fungal Infect., candidiasis<br>Fungal Infect., candidiasis<br>Fungal Infection |
| **Antihistamines** | H1- Blockers | Eczema, urticaria |
| **Antileprotic** | Dapsone | Dermatitis herpetiformis, leprosy, vasculitis |
| **Antimalarials** | Hydroxychloroquine | Lupus erythematosus, polymorphic light eruption, prophyria cutanea tarda |
| **Antivirals** | Acyclovir<br>Famciclovir | Herpes simplex/zoster<br>Herpes zoster, genital herpes simplex |
| **Corticosteroids** | Prednisolone usually | Bullous disorders, connective tissue disease, vasculitis |
| **Cytotoxics/ immunosuppressives** | Methotrexate<br>Hydroxyurea<br>Azathioprine<br><br>Cyclosporin<br>Gold | Psoriasis, sarcoidosis<br>Psoriasis<br>Bullous disorders, chronic actinic dermatitis<br>Psoriasis, atopic eczema<br>Bullous disorders, lupus erythematosus |
| **Retinoids** | Acitretin<br>Isotretinoin | Keratinization disorders<br>Acne |
| **Monoclonal antibodies (Biologics)** | Infliximab<br>Etanercept | Psoriasis with or without arthropathy |

### 2.1. Systemic Antifungal Agents

The prescription of systemic antifungals depends on their spectrum of action (see Table 4.7 and Table 4.8). Main indications for systemic antifungal drugs are

- chronic recurrent tinea disorder such as tinea pedis: dyshydrotic and hyperkeratotic forms,
- spreadinglesions in tinea capitis,
- acute tinea inflammation (vesicles, papules, pustules) as in tinea ungum (total dystrophic, proximal forms).

## Table 4.7 Systemic Antifungals and Their Spectrum of Action

| Agent | Spectrum of action | | |
|---|---|---|---|
| | **Dermatophytes** | **Yeasts** | **Molds** |
| Griseofulvin | +++ | - | - |
| Terbinafine | +++ | ++ | - |
| Itraconazol | +++ | +++ | +++ |
| Ketaconazol | ++ | + | - |
| Fluconazol | ++ | +++ | - |

## Table 4.8 Antifungalsfor Systemic Use

| Drug | Mechanism of action | Indications |
|---|---|---|
| **Terbinafine** | Inhibits sterol biosynthesis by blocking squalene peroxidase causing accumulation of squalene and cell death | Primarily dermatophytes (tinea corporis, tinea capitis, tinea pedis, tinea ungum) |
| **Griseofulvin** | Binds to tubulin, interfering with microtubule function thus inhibiting mitosis. The **micronized forms** are better absorbed and distributed | Dermatophyte infections (tinea capitis), not effective against yeasts and molds. Griseofulvin is still the only agent approved for **tinea capitis in children,** it has been replaced in most of its other uses by the more effective imidazoles. |
| **Itraconazole** | Inhibits cytochrome P450 – dependent synthesis of ergosterol, a key component of fungal cell walls. Because of its ability to inhibit cytochrome P450, caution should be used when considering interactions with other medications | Effective against dermatophytes, molds and many yeasts. Excellent against *Candida albicans* and *Candida krusei*; moderately effective against other *Candida* species, cutaneous mycoses, including onychomycoses, mycoses in HIV/AIDS, mucocutaneous and systemic candidiasis, recurrent vaginal candidiasis, aspergillosis, soft tissue mycotic infections. |
| **Fluconazole** | Inhibits cytochrome P450 – dependent synthesis of ergosterol, a key component of fungal cell walls | Effective against dermatophytes and yeasts; not molds. Effectiveness reduced against *Trichophyton mentagrophytes*, *Candida glabrata* and *Candida guilliermondii*. Useful for candidiasis in almost all settings from acute vaginal to HIV/AIDS to chronic mucocutaneous candidiasis, dermatophytes infections, including onycomycosis |
| **Ketoconazole** | Structurally similar to imidazole, and interferes with the fungal synthesis of ergosterol, a constituent of fungal cell membranes | Inhibits growth of dermatophytes (tinea criris, tinea corporis, tinea pedis) and yeast species such as *Candida albicans* |

## 2.2. Antihistamines

There are several types of antihistamine agents that bind to histamine receptors to inhibit their functions, $H_1$-receptor inhibiting drugs, widely used in dermatological treatment, are extremely effective in the treatment of allergic inflammatory skin disorders. Antihistamines suppress the histamine-induced wheal response (swelling) and flare response (vasodilatation) by blocking the binding of histamine to its receptors on nerves, vascular smooth muscle, glandular cells, endothelium,and mast cells. They exert a competitive antagonism to histamines. Itching and sneezing are suppressed by antihistamine blocking of $H_1$-receptors on nasal sensory nerves.

In common sense, the term *antihistamines* refers only to $H_1$-antagonists, also known as $H_1$-antihistamines. Sedation is a common side effect of first-generation antihistamines, such as diphenhydramine and doxylamine, which are also used to treat insomnia. However, second-generation antihistamines, such as loratadine, cetirizine, fexofenadine do not cross the blood-brain barrier, and as such do not cause drowsiness and also they have a long serum half-life.

The main indications for $H_1$-antihistamines in skin are suppression of pruritus in urticaria and atopic eczema, both of which are associated with increased mast cell numbers and tissue histamine levels.

**Table 4.9 Systemic Antihistamines**

| First generation (sedative) | Second generation (non-sedative) |
|---|---|
| Brompheniramine | Cetirizine hydrochloride |
| Chlorpheniramine | Fexofenadine hydrochloride |
| Clemastine | Loratadine |
| Cycloheptadone hydrochloride | Desloratadine |
| Dyphenhydramine | Levocabastine |
| Hydroxyzine hydrochloride | Mizolastine |
| Promethazine hydrochloride | Acrivastine |
| Promathazine teoclate | Levocetirixine dihydrochloride |
| Trimeprazine | |

## 2.3. Antileprotics

**Dapsone** is used extensively as a **first line agent in leprosy**.It also has important effects on several other diseases with no apparent common features (apart, perhaps, from the pathological involvement of polymorphs).It is a sulfone drug and sulfones are related to the sulfonamide family.

Dapsone has anti-inflammatory and immunomodulatory effects, which are thought to come from the drug's blockade of myeloperoxidase. This is thought to be its mechanism of action in treating **dermatitis herpetiformis.**

Dapsone is also useful in such diseases as linear IgA bullous dermatosis, bullous eruption of systemic lupus erythematosus and erythema elevatum diutinum, other

autoimmune bullous diseases (e.g. pemphigus foliaceus, bullous pemphigoid) and selected vasculitic syndromes.

## 2.4. Antimalarials

The most common antimalarials are chloroquine and hydroxychloroquine. The mechanism of action of the antimalarials is not well known. They exert various anti-inflammatory effects and they decrease platelet aggregation. The antimalarials are a second line therapy for cutaneous lupus erythematosus, after topical intralesional corticosteroids. They are especially useful in patients with widespread discoid lesions and in those with annular or papulosquamous lesions of subacute cutaneous lupus erythematosus. Other diseases are polymorphous light eruption, sarcoidosis, lichen planus.

## 2.5. Antiviral Agents

The systemic antiviral drugs are acyclovir, valacyclovir, cidofovir, famcyclovir, foscarnet sodium injections, gancycloivir.Acyclovir, valacyclovir and famcyclovir are all effective against herpes labialis when used intermittently or suppressively, and they are all effective in treating herpes zoster.
Intravenous acyclovir is used in immunocompromised patients with disseminated HSV or VZV and in patients with severe herpes zoster.
Famcyclovir is indicated for herpes zoster primarily or recurrent genital herpes, herpes suppression in immunocompetent patients and recurrent herpes simplex in HIV-infected patients.
Foscarnet is an intravenous antiviral used for CMV retinitis or CMV skin infection in HIV-infected patients and for acyclovir-resistant herpes simplex infections.

## 2.6. Cytotoxic/Immunosuppressive Agents

***Methotrexate***
Methotrexate (MTX) is and antimetabolite and a folic acid antagonist. It was first developed as an anticancer drug. MTX inhibits the synthesis of DNA, RNA, thymidylates, and proteins.Besides, it inhibits enzymes involved in purine metabolism, leading to accumulation of adenosine. MTX also exertsinhibition of T-cell activation and suppression of intercellular adhesion molecule expression by T cells, as well as selective down-regulation of B cells. Its use in severe, debilitating or recalcitrant, psoriasis is well established, where it is one of the most reliable agents available. MTX is also used in pityriasis rubra pilaris, pytiriasis lichenoides et varioliformis acuta (PLEVA), lymphomatoid papulosis, Reiter's disease, dermatomyositis and sarcoidosis, in certain types of vasculitis, neutrophilic and immunobullous dermatoses, in particular bullous pemphigoid.
The drug is associated with some side effects, notably marrow suppression and liver fibrosis, but these can generally be avoided if patients are monitored properly. Avoidance of alcohol and awareness of drug reactions is important.

***Azatioprine***

Azatioprine exerts moderately potent anti-inflammatory and immunosuppressive effects. It should be reserved for more serious, life-threatening or recalcitrant dermatoses after other therapies have failed. The active metabolite of azathioprine (6-thioguianine) inhibits purine metabolism and cell division. It has also other activities, which are not well understood, such as suppression of T-cell function and B-cell antibody production. It also decreases the number of Langerhangs cells in the skin and inhibits their ability to present antigen.

Azatioprine is most often used as a corticosteroid-sparing agent in the treatment of immunobullous diseases such as pemphigus vulgaris, bullous pemphigoid and cicatrical pemphigoid, cutaneous vasculitis, severe, recalcitrant atopic dermatitis and chronic actinic dermatitis in adults, connective tissue diseases such as systemic lupus erythematosus and dermatomyositis, it may improve the cutaneous manifestations as well. There may be a delay of 4-6 weeks in the onset of full clinical benefits.

***Cyclosporine***

Cyclosporine is a cyclic peptide of 11 amino acids, and has clinical immunosuppressive effects. Two forms are available, the original preparation (Sandimmune) and a predigested microemulsion (Neoral) that is more completely and consistently absorbed.

Cyclosporine binds to cyclophilin a member of the family of intracytoplasmatic proteins and the inhibitory action of thiese complex results in a decrease on the number of $CD4^+$ and $CD8^+$ (cytotoxic) T-cells in the epidermis.

Cyclosporine is best used on a short-term basis (< 6-12 months) to control flares of psoriasis and to provide an alternative to the patient's current regimen. It is reasonable to use cyclosporine as a sequential therapy with acitretin, methotrexate or other systemic therapies. After psoriasis clearance has been initiated by cyclosporine, the alternative medicine may be started and advanced to the therapeutic dose. At the same time, cyclosporine may be weaned by 1 mg/kg/day each month until the patient is receiving acitretin or methotrexate alone.

Cyclosporine can be beneficial for patients with psoriasis who have failed or cannot tolerate other therapies and for those with widespread atopic dermatitis, severe pyoderma gangrenosum.

## 2.7. Retinoids

The retinoids are a class of chemical compounds that are related chemically to vitamin A. Retinoids include naturally occurring molecules and synthetic compounds that have specific biologic activities resembling those of vitamin A or bind to the nuclear receptors for retinoids.

There are three generations of retonoids:

- **First generation retinoids** include retinol, retinal, tretinoin (retinoic acid), isotretinoin, and alitretinoin.

- **Second generation retinoids** include etretinate and its metabolite acitretin.
- **Third generation retinoids** include bexaroyene, tazarotene and adapalene.

The biological functions and actions of retinoids**:**

1. Reproduction, embryonic growth and morphogenesis
2. Modulation of proliferation and differentiation of epithelium.
3. Decreae in sebaceous gland size (isotretinoin)
4. Immunological and anti-inflammatory effects
5. Tumor prevention and treatment
6. Effect on extraxellular matrix components.

Systemic treatment with acitretin is effective in several disorders of keratinization. Darier's disease, ichtyosis vulgaris, congenital ichtyosis (particularly dry lamellar type, various types of palmoplantar keratoderma, and also erythrokeratoderma figurate variabilis today represent standard indication for oral acitretin treatment.

Oral acitretin belongs nowadays to the mainstream systemic antipsoriatic treatment, particularly in severe pustular and erythrodermic types of the disease. It acts on a pathological epidermis to reduce proliferation and stimulate differentiation. Acitretin is usually prescribed in combination with other modalities (mild corticosteroids, dithranol, tar, vitamin D derivatives) and/or with phototherapy (Re-PUVA). Palmoplantar pustulosis, psoriasis of nails, HIV-associated psoriasis significantly improve under systemic acitretin. In pityriasis rubra pilaris, a beneficial effect can be expected under systemic acitretin, especially on juvenile type of the disease.

Oral isotretioin is only one drug currently available that affects all four pathogenic factors of acne, directly suppressing abnormal desquamation of sebaceous follicle epithelium and sebum production. The basic patterns of use of retinoids are described in Table 4.10.

**Contraindications**: pregnancy, breast-feeding

Pregnancy is recommended to be excluded in female patients two weeks prior to commencement of **isotretinoin**, and patients should use two simultaneous forms of effective contraception at least one month prior to commencement, during and for at least one month following **isotretinoin** therapy, women of childbearing age should either abstain from sexual intercourse or use 2 effective methods of birth control for at least 1 month before, while taking and for 3 years after taking **acitretin**.

**Table 4.10 Retinoids in Dermatology**

| Retinoids | Skin disorder | Clinical forms |
|---|---|---|
| **Isotretinoin** | **Acne** | Nodulocystic<br>Severe scarring<br>Severe acne-associated psychological distress |
| **Isotretinoin** | **Rosacea** | Nodulocystic<br>Papulo-pustular |
| **Acitretin**<br>**Etretinate** | **Psoriasis** | Palmo-planter puslular<br>Pustular generalized<br>Erythrodermic<br>Psoriasis of nails |
| **Acitretin** | **Lichen planus** | Oral and skin forms |
| **Etretinate** | **Cutaneous T-cell lymphoma** | Sezary syndrome with no organ involvement |
| **Bexaroten** | | Early Ia,IB, IIA stages |
| **Alitretinoin** | **Sarcoma Kaposi** | |
| | **Epithelium tumor** | |
| **Acitretin** | **Ichtyosis** | Lamellar ichtyosis<br>X-linken ichtyosis<br>Epidermolytic ichtyosis<br>Ichtyosis vulgaris |
| **Acitretin**<br>**Isotretinoin** | **Darier's disease** | |
| **Etretinate** | **Pityriasis rubra pilaris** | |
| **Acitretin**<br>**Etretinate** | **Lichen sclerosus and atrophicus** | Genital region localization |
| **Alitretinoin** | **Chronic hand eczema**<br>**Seborrhea** | |

## 2.8. Biologics

Biologics are novel compounds composed of antibodies or other peptides that act through one of three mechanisms: inhibiting inflammatory cytokine signaling (typically tumor necrosis factor or TNF), inhibiting interleukins, T-cell activation, or depleting B-cells. They are being used more frequently to treat a multitude of systemic inflammatory conditions. In the past ten years biologic drugs have emerged as an important advance in the treatment of inflammatory diseases such as rheumatoid arthritis, juvenile idiopathic arthritis, ankylosing spondylitis, psoriatic arthritis, plaque psoriasis, Chron's disease and ulcerative colitis.
Biologics are divided into three groups:

1. **Recombinant human cytokines and growth factors** (interferon-α [INF-α], interferon-γ [INF-γ], interleukin 1 receptor antagonist [IL1Ra], interleukin 2 [IL-2], interleukin 4 [IL-4], interleukin10 [IL-10], interleukin 11 [IL-11],granulocyte macrophage colony stimulating factor [GV-GSF], platelet derived growth factor [PDGF].

**2. Monoclonal antibodies**

– Anti TNF-α: infliximab, adalimumab,certolizumab,golimumab
– Anti-LFA1: efalizumab
– Anti-CD20: rituximab
– Anti-IL-12 and anti-IL-23 monoclonal antibody: ustekinumab
– Anti-CD2 antibody: siplizumab
– Anti-CD4 antibody: orthoclome (OKTcdr4a)
– Anti-CD25 antibodies: basiliximab, daclizumab
– Anti-CD80r: galiximab (IDEC 114)
– Anti-IgE: omalizumab

3. **Fusion antibody proteins** (chimeric proteins)

– Etanercept
– Alefacept
– Abatacept

**Infliximab** (a chimeric monoclonal anti-TNF antibody), **adalimumab** (a fully human anti-TNF monoclonal antibody) and **etanercept** (a recombinant soluble decoy TNF-receptor) exert therapeutic effects via the suppression of TNF-α, a cytokine released by macrophages that is central to cell-mediated immunity.
**Ustekinumab** is a fully human monoclonal antibody that binds with high specificity and affinity to the cytokines interleukin -12 and IL-23 thereby suppressing IL-12 and IL-23-mediated inflammation associated with psoriasis.

## 3. Phototherapy and Photochemotherapy

Phototherapy is nowadays one of the main methods used in dermatology. It can be used alone or in combination with oral and/or topical treatment. The action of ultraviolet radiation is exploited for the treatment of many diseases. The detection of the type of skin isvery important in the appointment of phototherapy. The classification of skin types known as the Fitzpatrick skin type (or phototype) depends on the amount of melanin pigment in the skin (see Table 4.11) and helps the doctor to prescribe phototherapy.

**Table 4.11 Skin Types**

| Skin Type | Typical features | Tanning ability |
|---|---|---|
| **I** | Pale, white skin, blue/hazel eyes, blond/red hair | Always burns, does not tan |
| **II** | Fair skin, blue eyes | Burns easily, tans poorly |
| **III** | Darker white skin | Tans after initial burn |
| **IV** | Light brown skin | Burns minimally, tans easily |
| **V** | Brown skin | Rarely burns, tans darkly easily |
| **VI** | Dark brown or black skin | Never burns, always tans darkly |

Dermatologists have been used various forms of light treatment for years in the management of psoriasis, eczema and vitiligo. The range of conditions for which

various regimens are used has increased significantly over the last few years and now includes, paradoxically, some of the photodermatoses.
Ultraviolet light is divided to three wavelength ranges. From longest to shortest, they are UVA (320 nm till 400 nm), UVB (290 nm till 320 nm), und UVC (200 nm to 290 nm). The shorter wavelength the lower is the penetration and the greater the energy of light. UVA and UVB directly or indirectly damage DNA by exciting UV light absorbing molecule or they produce free radicals that injury cells.
The following types of phototherapy are used for dermatological purposes:

- UVB-therapy
- UVA1 long wave therapy
- Photochemotherapy (PUVA)
- Photodynamic therapy
- Laser therapy

## 3.1. UVB-Therapy

UVB-therapy (290 nm till 320 nm) is the type of immunosuppressive therapy that inhibits the function of Langerhance cells. **Narrowband UVB-therapy (311 nm)** is thought to be more effective than broadband UVB in the treatment of skin diseases. **Indications forUVB therapy** are vitiligo, psoriasis, pityriasis lichenoid chronica, atopic dermatitis, lichen planus, alopecia areata, pruritus, mycosis fungoides.
UVB (290-320 nm) is given 3 times a week. The initial dose is determined from the patient's skin type or *minimal erythema dose* (MED). With each visit, the scheduled dosage is increased. Commonly, 10-30 treatments are the normal course. UVB can be used in children and pregnant women. Side effects include acute sunburn and increase risk of skin cancer.

## 3.2. UFA 1 Long Wave Therapy (340 nm-400 nm)

Unlike UVB radiation that can penetrate at the most into the papillary dermis, longer wavelengths in the UVA region have the capacity to reach the subcutis as well. Accordingly, as well as due to its lesser antiproliferative activity, UVB has not been established in the treatment of sclerotic disorders excerpt foe occasional cases of graft-versus-host disease (GvHD).
UVA 1 irradiation has been shown to initiate atopic cell death in dermal T-lymphocytes and dermal immunoregulation. Besides, UVA1 irradiation induces the formation of several cytokines and soluble factors, e.g. interleukin-1 and/or interleukin-6 stimulating the synthesis of collagenase. Indications for UVA1 long wave phototherapy are lupus erythematosus, scleroderma, exacerbated atopic dermatitis, cutaneous T-cell lymphoma, parapsoriasis or mucinosis follicularis, polymorphic light eruption, actinic prurigo, cutaneous porphyrias.

## 3.3. Photochemotherapy (PUVA)

UVA alone has minimal effect, thus it is used in combination with photosensitizing psoralens given topically or systemically. PUVA stand for **P**soralens plus **U**ltra**V**iolet **A**. Commonly, oral 8-methoxypsoralens is taken 2 hours before UVA (320-400 nm). The psoralen is photoactivated, which results in DNA cross-linking, inhibition of cell division, and suppression of cell-mediated immunity. Like UVB, the initial dose of UVA is determined by MED or skin type; and dosage is increased a scheduled visits. PUVA is usually given 2-3 times per week for 15-25 treatments. PUVA can be combined with acitretin (RePUVA) but not methotrexate. *Bath PUVA*, bath containing a psoralen, is an alternative to systemic-side effects of oral psoralens.*Local PUVA*, topical psoralen, may be effective in psoriasis and dermatitis involving the hands or feet. PUVA may be given for psoriasis, mycosis fungoides, atopic eczema, polymorphic light eruption or vitiligo. Acute side effects include pruritus, nausea, erythema; long-term side-effects of premature skin ageing and skin cancer depend on the number and total dose of UVA. Cataracts are possible and UVA-opaque sunglasses must be worn for 24 hours after taking psoralen.

## 3.4. Photodynamic Therapy

Photodynamic therapy (PDT) is used clinically to treat a wide range of medical conditions, including age-related macular degeneration and malignant cancers, and is recognizedas a treatment strategy which is both minimally invasive and minimally toxic. PDT uses exogenously administered or endogenously formed photosensitizers activated by light to induce cell death via formation of sunlight oxygen and other free radicals.

Photodynamic therapy is a 2-step procedure. In the first step, the photosensitizer is administered to the patient by one of several routes (e.g. topical, oral, intravenous), and it is allowed to be taken up by the target cells. The second step involves the activation of the photosensitizer in the presence of oxygen with a specific wavelength of light directed toward the target tissue. Because thephotosensitizer is preferentially absorbed by hyperproliferative tissue and the light source is directly targeted on the lesional tissue, photodynamic therapy achieves dual selectivity, minimizing damage to adjacent healthy structures. For dermatological purposes, incoherent lamps or light emitting diode arrays can be used for lightactivation.

The basis of PDT is the interaction of light with photosensitive agents to produce an energy transfer and a local chemical effect. Beyond direct phototoxic effects on target tissue, photodynamic therapy with various photosensitizers has been shown to modify cytokine expression and induce immune-specific responses. Immunologic effects include the production of interleukin-1 beta, interleukin 2, tumor necrosis factor-alpha, and granulocyte colony-stimulating factor. Photodynamic therapy generally has a low potential for causing DNA damage, mutations, and carcinogenesis. Photosensitizers used for PDA are 5-aminolevulinic acid (ALA), methyl ester of ALA. **Indications for PDT in dermatology** are basal

cell carcinoma, Bowen disease, squamous cell carcinoma, actinic keratosis, malignant melanoma, mycosis fungoides, Kaposi sarcoma. Non-tumoral applications of ALA-PDT are psoriasis, acne vulgaris, viral warts, alopecia areata, photoaging.

### 3.5. Laser Therapy

**Laser – L**ight **A**mplification by **Stimulated** Emission ofRadiation – produces high energy radiation.
Lasers used in dermatology emit specific wavelengths within the UV (10-400 nm), visible (400-720 nm) and infrared (IR) (720 -1 000 000 nm) portions of the electromagnetic spectrum. By the active medium type lasers are divided into solid (ruby, neodymium), gas (He-Ne, $CO_2$), semiconductor (or diode), liquid (for inorganic and organic dyes), metal-vapor lasers (the most common: a copper vapor or gold).
In dermatology, lasers of the two types are used: low-intensity lasers – for laser therapy and high intensity ones – for laser surgery.
Low-intensity laser radiation has the following effects: anti-inflammatory, antioxidant, anesthetic, immunomodulatory, and used to treat atopic dermatitis, psoriasis, alopecia areata. The penetration of the laser radiation depends on wavelengths, decreasing from the long to the short wave radiation.
High-intensity is obtained using $CO_2$-laser, Er: YAG laser and argon laser.CO2-laser is used mainly in dermatology and cosmetology for laser removal (destruction) of nevi, warts, tumors, scars and for dermabrasion.
Relative contraindications for the use of laser therapy are cancer, diabetes mellitus, hypertension, hyperthyroidism, arrhythmias.

## 4. Basic Surgical Procedures

**Excisional Biopsy**. Excision axis depends on skin creases/Langer's lines and its margins on the lesion. Once the skin is numbed with local anesthetic, the skin is incised vertically down to the subcutaneous fat with the scalpel, in a smooth continuous manner to complete both arcs of the ellipse. Using simple interrupted skin sutures, the wound is apposed and slightly everted. Absorbable subcutaneous sutures are used for big excisions.
**Incisional Biopsy**.Performed for diagnostic purposes. The technique is comparable to an excision, but less tissue is taken.
**Punch Biopsy.** A punch (normally about 4 mm in diameter) is twisted into the skin: resulting cylinder of skin is removed and the defect cauterized or sutured.
**Shave Biopsy.** Used for benign lesions, usually intradermal nevi or seborrheic keratosis. The lesion is shaved parallel to and slightly above the skin's surface. Cautery may be used to achieve hemostasis. Skin tags are removed by using scissors to snip them off followed by cauterization to any bleeding points.
**Curettage.**After local anesthetic, the lesion is removed by a gentle scooping motion with the curette. The base is then cauterized. Curettage may be used in

seborrheic keratosis, pyogenic granulomas, keratoacanthomas, single facial viral warts, but not nevi.

**Cautery.**Provides hemostasis and destroys tissue. The classic cautery machine has an electrically heated wire and is self-sterilizing. Silver nitrate sticks or 35% aluminum chloride in 50% isopropyl alcohol provide chemical cautery.

**Cryotherapy.**Liquid nitrogen (- 196 °C) is delivered by cotton wool bud or spray gun and injures cells by ice formation. After immersion into liquid nitrogen, the cotton wool bud is applied to the lesion for 10-15 seconds until a thin frozen halo appears at the base. The spray gun is used at a distance of 10 mm for a similar amount of time. Longer freezing times are given for malignant tumors. Blisters may develop within 24 hours. These are punctured and a dry dressing applied. Side effect may include hypopigmentation of pigmented skin, ulceration (especially on the lower legs of the elderly). Treatment may be repeated in 4 weeks if warranted. Cryotherapy may be used for viral warts, seborrheic keratosis, molluscum contagiosum, intraepidermal carcinoma.

**Mohs' Surgery.**Excision of malignant tumor which is mapped and microscopically examined to define its extent and the completeness of the excision.

**Dermabrasion**. A rotating mechanical head wounds the skin down to the dermis.

**Laser (Light Amplification by Stimulated Emission of Radiation)**. High intensity light energy is applied to the tissue. Laser surgery is a rapidly changing field in which new types of lasers, as well as the conditions amenable to treatment, are continually being introduced. Lasers vary from a continuous-wave carbon dioxide laser to a short-pulsed pigment Q-switched ruby laser.Uses for lasers are equally varied and include: port wine stain nevi, telangiectasia, viral warts, some tumors, and tattoos.

# V. FUNGAL INFECTIONS

## 1. Introduction

Fungi are amongst the most successful and widely distributed of microorganisms with habitats ranging from lakes to the Arctic wastes. They are classified as a separate kingdom of living organisms and have several distinct structural and physiological features: unicellular or filamentous growth; saprophytic or parasitic existence; a polysaccharide-based cell wall; and single or multiple nuclei.
Fungal cells may also be specialized for certain functions, chiefly propagation as spores, but also for penetration of underlying structures, such as plant cells or hairs. The basic fungal cell is illustrated in Fig. 5.1.

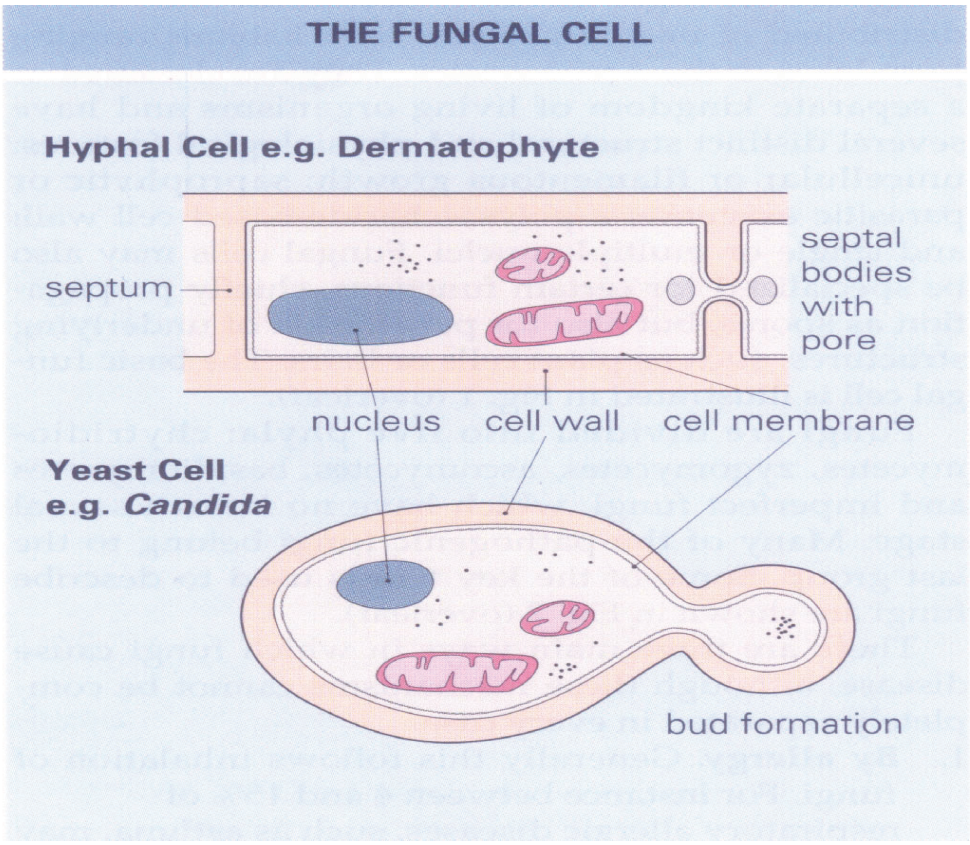



**Fig. 5.1.Fungal Cell**

Fungi are divided into five phyla: chytridiomycetes, zygomycetes, ascomycetes, ascomycetes, basidiomycetes and imperfect fungi, which have no known sexual stage. Many of the pathogenic fungi belong to the last group.
There are three main ways in which fungi cause disease, although these mechanisms cannot be completely separated in every case:
**1. Allergy.** Generally this follows inhalation of fungi. For instance between 4% and 15% of respiratory allergic diseases, such as asthma, may be caused by fungi.

**2.Toxins.** The effects of the fungal toxins to be described such as the ergot alkaloids from the ergot of rye, *Claviceps purpurea*, or muscarine from the toadstool, *Amanita muscaria*, have been known for centuries. More pharamacologically active toxins, such as the aflatoxins, ochratoxins or trichothecenes, have been discovered more recently bit they may also cause human disease, for example hepatic necrosis. These toxins may be produced in small but significant levels in contaminated grain.

**3**. **Invasion of tissue** – the mycosis. Skin disease ascribed to fungi generally follows tissue invasion either from the external surface or by implantation via a superficial injury or following internal dissemination from a deep focus of infection.

They are known respectively as the **superficial, subcutaneous** and **systemic mycosis** (see Table 5.1). Immunological reactions due to the presence of fungi may contribute to the pathology of fungal disease. This can occur either at the site of the infection, for instance in the formation of granulomas, or by transepidermal elimination, or at a distance, by causing skin diseases, such as erythema nodosum, urticaria or vesicular eczema (pompholix). Few mycotoxins affect the skin but some trichothecenes may cause epidermal necrosis.

**Table 5.1.Types of Fungal infections – the Mycosis**

| | |
|---|---|
| **Superficial mycosis** | **Dermatophyte** or ringworm infections<br>***Malassezia*infections** (pityriasis versicolor, *Malassezia* folliculitis)<br>**Superficial candidosis**<br>Others: infections dues to *Scyralidum*<br>white piedra<br>black piedra<br>tinea nigra |
| **Subcutaneous mycosis** | **Mycetoma**<br>**Chromoblastomycosis, phaeohyphomycosis**<br>**Sporotrichosis**<br>Others; lobomycosis<br>subcutaneous zygomycosis |
| **Systemic mycosis** | **Infections caused by endemic respiratory pathogens**:<br>histoplasmosis<br>coccidioidomycosis<br>blastomycosis<br>paracoccidioidomycosis<br>Rare: infections due to Penicillinum marneffei<br>**Infections due to opportunistic fungi:**<br>Candidosis<br>Aspergillosis<br>Zygomycosis<br>Cryptomycosis<br>Rare: infections due to:<br>Fusarium<br>Hansenula<br>Trichosporon |

## 2. Pathogenesis

### Skin invasion

Certain fungi are able to penetrate keratinized cells by producing enzymes such as keratinases. *Trichophyton mentagropjytes*, for instance, has at least two enzyme isotypes. In addition, hyphae are able to "squeeze" between keratinocytes. Other fungi which cause skin disease have not been shown to produce keratin-splitting enzymes. *Candida albicans* elaborates a proteinase which is important for determining virulence and strains which do not produce this enzyme are less virulent in experimental infections. *Malassezia* species produce lipases which may aid the digestion of fats in sebum. Fungi which cause nail disease do not all produce keratinases and some appear to be able to invade the nail plate only if there is a pre-existing abnormality, such as peripheral vascular disease.

The process of invasion of skin depends on a number of factors:

1. Survival of infective spores (arthtospores) in the environment before transmission. Many dermatophytes survive for over two years in shed skin scales.
2. Adhesion of fungal cells to the skin scales. This depends on a time – dependent physicochemical bond between a fungal cell-wall receptor and keratinocytes or mycosal cells.
3. Skin surface factors such as pH and carbon dioxide tension.

The defenses against fungi invading skin are shown in Table 5.2.

**Table 5.2.The Defenses Against Fungi Invading Skin**

| |
|---|
| **Non-immune mechanisms** |
| Serum inhibitory factors including unsaturated transferring |
| Fatty acids in sebum |
| Increased epidermal cell turnover |
| Phagocytosis by neutrophils and macrophages |
| **Immune mechanisms** |
| T-lymphocutes activation – via cytokines, e.g. gamma interferon, TNF (tumor necrosis factor) |
| (Possible role for antibody in opsonization and secretory IgA in mucosal candidosis) |

The way in which lymphocytes activation leads to elimination of fungi in epidermis is unknown but cytokine-mediated cooperation between neutrophils and macrophages and increased epidermal cell turnover are involved.

Small changes in host defense are important for allowing organisms to invade the skin or mucous membranes (see Table 5.3). This means that although not all fungi should be regarded as opportunistic pathogens, changes in host resistance will make a difference to the outcome and clinical presentation of most fungal infections.

The existence of a pre-disposing factor in the host will not necessarily lead to an increased frequency of infection as this also depends on exposure to the infecting organisms. In AIDS, for instance, oropharingeal candidosis is very common as *Candida* is normally an oral commensal, but dermatophytosis does not have an increased incidence, presumably as the frequency of exposure does not increase.

However, clinical manifestations of dermatophytosis in AIDS patients often differ to those seen in other groups.

**Table 5.3 Factors Associated with Fungal Infections**

| Factor | Infection |
|---|---|
| Age – infancy, old age | Candidosis |
| Pregnancy | candidosis |
| Epithelial abnormalities | candidosis<br>dermatophytosis |
| Endocrine disease | candidosis<br>dermatophytosis<br>pityriasis versicolor<br>zygomycosis |
| Antibiotic therapy | candidosis<br>aspergillosis |
| Immunosuppression (drugs,congenital, cancer) affecting: | |
| neutrophils | candidosis<br>aspergillosis<br>zygomycosis |
| T-lymphocytes | most except<br>aspergillosis<br>zygomycosis |
| Zinc deficiency | candidosis |
| Iron deficiency | candidosis |

The reasons for increased incidence of infection in the presence of certain predisposing factors are varied.
**Antibiotics** reduce the local bacterial flora, which compete for adherence sites.
**Diabetes mellitus** increases levels of available sugars in tissues and reduces phagocytes efficiency.
**Smoking** reduces ciliary clearance of inhaled fungal particles.

## 3. Epidemiology

The spread of fungal infections depends on a number of factors:
presence of the organism
its survival in a form suitable for infection
route of entry.
There are two main sources of infection in man: endogenous and exogenous. The endogenous infections are caused by fungi which are part of the resident microflora such as *Candida* and *Malassezia* yeasts. Infection then follows some change in the host which allows the fungus to change from saprophyte to parasite.

The other fungal pathogens are exogenous organisms. Dermatophytes may originate from one of three main sources: animals (**zoophilic**), soil (**geophilic**) and other humans (**antropophilic**). All the subcutaneous pathogenic fungi are soil or plant organisms; the world distribution of infections depends on their distribution in nature.

Whether one of these organisms causes infection depends on host susceptibility which, in turn, is largely determined by the immune status of the host or the presence of other risk factors, i.e. sources of infection (see Table 5.4).

Genetic susceptibility has been proposed in those infections where fungi invade without underlying host predisposition. The best evidence for this comes from only one disease, tinea imbricata, a dermatophyte infection caused by fungi called *Trichophyton concentricum*. This is based on a population genetic analysis of the prevalence of infection in families in the highlights of Papua New Guinea.

**Table 5.4Sources of Fungi**

| **Organism** | **Source** |
|---|---|
| Dermatophytes | humans, soil, animals |
| *Madurella mycetomatis* | plants, thorns |
| *Sporothrix schenckii* | plants, moss, soil |
| *Histoplasma capsulatum* | soil (bird and bat excreta) |
| *Coccidioides immitis* | new world semi-dessert soil |
| *Aspersillus* | building work, AC systems, hospital equipment, e.g. ventilators, plants |
| Zyhomycetes | building work, compost heaps |
| *Rhizopus rhizopodiformis* | dressing packs, bandages |
| *Cryptococcus neoformans* | soil, pigeon excreta, red gum trees |

The procedures for investigating the epidemiology of fungal disease are simple (see Table 5.5).

**Table 5.5 Investigation of the Epidemiology of Mycoses**

| |
|---|
| **Superficial mycoses** |
| • Presence of cases |
| • Culture to confirm source |
| • (Wood's light – dermatophytes only) |
| **Subcutaneous mycoses** |
| • Presence of cases |
| • Culture of cases and environmental sources |
| • (Skin testing – for delayed-type hypersensitivity- sporothrichosis only) |
| **Systemic mycoses** |
| • Presence of cases |
| • Autopsy findings or surgical removal of pulmonary nodules |
| • Skin testing (histoplasmosis, coccidioidomycosis, paracoccidioidomycosis) |
| • Environmental sampling – choose suitable sites |

## 5. Superficial Fungal Infections

The superficial fungal infections (mycoses) are the commonest of the human fungal infections and they include derpatophytosis or ringworm, superficial *Candida* and *Malassezia* infections as well as rare conditions such as tinea nigra and black or white piedra. Superficial infections rarely involve deep tissue except in candidosis – although even here most infections arising on the skin or oral mucosa will never invade more deeply.

## 5.1. Dermatophyte Infections

The dermatophyte or ringworm fungi are hyphal organisms which invade the stratum corneumof the epidermis and keratinized tissues such as hair or nail derived from it. The dermatophytes affecting man belong to three genera - *Trichophyton, Microsporum* and *Epidermophyton*. They can be divided into those infections which are spread from man to man (**anthropophilic**), animal to man (**zoophilic**) or soil to man (**geophilic**). The commonest of these organisms is *Trichopyton rubrum* followed by *T. violaceum*, *T. interdigitale/mentagrohytes*, *Microsporum canis* and *M. audoinini*. However, this pattern differs in different countries. For instance, the order of frequency most often seen in the United Kingdom and Europe is shown in Table 5.6. However, with specific infections such as tinea capitis the causes of disease in different countries are strikingly different, as shown in Table 5.7.

**Table 5.6 Dermatophytes in the UK and Europe in Order of Frequency of Isolation**

| Frequent isolates | Infrequent isolates |
|---|---|
| *Microsporum canis*<br>*Trichophyton rubrum*<br>*T. interdigitale*<br>*Epidermophyton floccosum*<br>*T. verrucosum*<br>*T. mentagrophytes* (animal source) | *T. erinacei*<br>*T. soudanense*<br>*T. viloaceum*<br>*N. equinum*<br>*M. gypseum* |

**Table 5.7Main Casual Agents for Tinea Capitis in Different Geographic Areas**

| Europe | North America | Africa | India |
|---|---|---|---|
| *M. canis*<br>*T. tonsurans* | *T. tonsurans*<br>*M. canis*<br>*M. audouinii* | *T. violaceum*<br>*T. soudenense*<br>*M. audouinii*<br>*M. canis*<br>*T. yaoundei* | *N. violaceum* |

Dermatophyte infections occur in any patient irrespective of age or sex. Generally scalp infections are not seen in adults except rarely in women, and tinea pedis is uncommon under the age of ten.

**Epidemiology**

Animal or zoophilic infections are usually sporadic and restricted to the areas where the host animal is found. *Microsporum canis,* the cat and dog ringworm, is the commonest of the zoophilic infections world-wide and spread occurs directly from an infected animal, and possibly from furniture, floors and carpets in the home of an infected animal. Anthropophilic dermatophytes are more common in the community and in some cases there is evidence to support the existence of localized epidemics of infection where there are appropriate conditions for transmission. These are seen in swimming baths, school changing areas and industrial shower rooms or areas where infected skin scales can be shed on wet floors. Spread of dermatophyte infections has led to a heavy rate of infection in coal miners in Europe where, in some mines, the infection rate is 35% or more. Bacterial infection is also common in this group and may follow dermatophytosis.

Tinea capitis, a childhood infection, is often a sporadic infection caused predominantly by zoophilic organisms such as *Microsporum canis*. However, in some parts of Europe, Asia and Africa, certain urban areas in the USA as well as other parts of the world, epidemics of this infection have been described affecting large numbers of children and caused by anthropophilic organisms. Transmission can occur following a short contact with an infected child.

Nail infections caused by dermatophytes are common in the community. Studies from the United Kingdom suggest that about 2.7% of the population have onychomycosis, with an incidence of infection approaching 5 per 1,000 each year. At least 50% of these do not present for treatment.

**Pathogenesis**

The initial infection probably follows contact with an infected desquamated scale or hair. The process of skin invasion is initiated by adherence of the atmosphere to the stratum corneum. It then germinates and penetrates keratinocytes.

**Pathology**

Most dermatophyte infections are confined to the stratum corneum or specialized keratin structures such as hair or nail. In the skin the infection seldom passes the granular layer unless there is hair follicle invasion, in which case fungal fragments are surrounded by phagocytes or giant cells in the dermis in the vicinity of a destroyed follicle. In many infections the main feature is a lymphohistiocytic infiltrate around the upper dermal blood vessels, the fungus in the upper layers of the epidermis only being visible with special strains such as Periodic Acid Schiff. In more inflammatory lesions, the early phase, there is a dense neutrophil accumulation around hair follicles.

**Clinical features**

The archetypical lesion of a dermatophyte infection is the ringworm or tinea circinata. This is a round scaly lesion whose rim is more inflamed and scaly than the center. Typically this form occurs in infections of the body, **tinea corporis**.

Dermatophyte infections are normally called "**tinea**" followed by the appropriate part of the body involved (in Latin). Other forms include **tinea pedis, tinea corporis, tinea cruris, tinea capitis** and **tinea facei**. Nail infections, **tinea unguium**, are also called **onychomycosis due to dermatophytes**. **Tinea incognito** describes an atypical dermatophyte infection often located on the face and usually associated with the inappropriate use of topical corticosteroids as therapy.

### 5.1.1. Tinea pedis

Tinea pedis is the commonest dermatophyte infection most often caused by anthropophilic fungi such as *Trichophyton rubrum* and *T. interdigitale (mentagrophytes)*. The earliest lesion develops with scaling and itching between the toes, particularly the lateral third and fourth interdigital spaces; this may spread to the undersurface of the toes.

– Blisters are generally only seen with *T. interdigitale.*

– In *T. rubrum* infections, the soles are often covered with a dry scaly rash – "dry" or "moccasin" – type dermatophytosis

– In chronic cases,erosion of the skin of the toe webs may enlarge with the appearance of a greenish discolouration due to Gram negative bacteria such as *Pseudomonas*

Various causes of interdigital scaling are shown in Table 5.8.

**Table 5.8Causes of Interdigital Scaling**

| | **Dermatophyte** | **Candida** | **Gram-negative** | **Erythrasma** | **Staphylococcus Aureus** |
|---|---|---|---|---|---|
| **Symptomps** | itch, scaly | soggy, eroded | sore, eroded | scaly | itchy |
| **Site** | lateral toe webs | lateral toe webs | lateral toe webs | lateral toe webs | first toe web |
| **Colour** | red/white | white | green/white | red/white | red |
| **Spread** | soles, nail | no spread | no spread | no spread | dorsum |

### 5.1.2. Tinea cruris

Tinea cruris presents with scaling in the groin extending onto the upper surface of the thigh and around the perineum; it is mainly seen in adult men. The infection is generally bilateral and itchy. There is often a raised margin and the infection may extend around the natal cleft to the perineum. Other causes of groin rash include erythrasma (a bacterial infection) and candidosis. In erythrasma the skin is uniformly affected with fine wrinkles and scales and has a light red/brown colour. The presence of papules or pustules outside the border (satellite pustules) is characteristic of *Candida* infection. A summary of the causes of scaling in the groin is given in Table 5.9. Flexural psoriasis may also produce scaling in this area with erythematous and soggy skin, but usually there are psoriatic lesions elsewhere, e.g. around the umbilicus.

**Table 5.9Causes of Scaling in the Groin**

| | **Dermatophyte** | **Candida** | **Erythrasma** |
|---|---|---|---|
| **Symptoms** | Itch | Itch +/- | Itch +/- |
| **Signs** | Scaling<br>prominent rim | Satellite pustules | Uniform fine scaling |
| **Colour** | Red | Deep red | Brown/red |
| **Spread** | Perineum<br>nails<br>feet | Perineum | axillae |

### 5.1.3. Tinea corporis

Tinea corporis may either be caused by zoophilic fungi or anthropophilic organisms, and more rarely by geophilic fungi. Lesions are annular, often irregular and may be multiple. The edge in at least one area is clearly seen and the hair follicles are prominent. Generally, in infections caused by zoophilic dermatophyrtes the lesions are more inflamed and itch severely; with anthropophilic fungi such as *Trichophyton rubrum* the lesions are often large, have a poorly defined border and there is less erythema or scaling.Tinea corporis is often confused with other annular lesions such as eczema, annular erythemas, psoriasis, and granuloma annulare.

The distinguishing features of tinea corporis are:

- Annular shape – the edge is more distinct than the rest of the lesion in at least one area
- Scaling is more obvious at the edge
- Itch
- Hair follicles within the margin are often prominent

### 5.1.4. Tinea capitis (scalp ringworm)

Tinea capitis usually presents in childhood with patches of scalp-hair loss and scaling. There is a background of erythema, although in some children this is minimal. The intensity of inflammation varies although the zoophilic fungi usually produce more crusting and oozing. At its most extreme this type of inflammatory lesion affecting a hear-baring area is boggy and pustular, a **kerion,** which is an inflammatory response to the dermatophyte itself rather than a secondary bacterial infection. Hair loss is seldom permanent unless an extensive kerion forms and even then there is a surprising degree of recovery. The severity of itching is very variable.

There are three main patterns of scalp infection which are generally classified by the way in which the dermatophytes form spores after invading the hair shaft: **ectothrix, endothrix** and **favic.** These patterns, in part, determine the site of breakage of hairs and the clinical appearances. They are best determined by careful microscopic examination of infected hairs.

## Table 5.10Types of Tinea Capitis

| | Ectothrix | Endothrix | Favic |
|---|---|---|---|
| **Clinical** | erythema, scaling | often less inflammation | mixed, crusting |
| **Level of hair break** | 1-3 mm above scalp | scalp level | may not break |
| **Source** | animals or children | children | children |
| **Commonest in** | Europe, urban tropics (some) | USA, rural tropics Europe (some) | sporadic |
| **Hair changes** | spores outside hair | spores in hair | all spaces in hair |

It is possible to form some preliminary understanding of the likely source of infection by the clinical and microscopic features which will focus the subsequent investigation. The final decision will rest on the results of culture. In Europe, for instance, the commonest organism is *Microsporum canis*, a cause of ectothrix infection while in many cities in the USA *Trycophyton tonsurans* is the dominant fungus.

Favus is now a rare infection seen in small foci in the USA, North Africa and the Middle East. It is caused by *Trichophyton schoenleinii*. It is clinically important as it may

- present with multiple crusts or scutula in the scalp
- cause scarring alopecia
- affect adults (mainly women) in addition to children.

Some preliminary help with the diagnosis can also be obtained by shining a filtered ultra-violet light on lesions – Wood's light. *Microsporum* but not *Trychophyton* species fluoresce green when viewed with this lamp in a completely darkened room. In favus, hairs have a dull yellowish fluorescence. Wood's light can also be used to select infected hairs for culture. Features of tinea capitis associated with different organisms are shown in Table 5.11.

Scalp scaling without hair loss occurs in a number of conditions. In children, seborrhoeic dermatitis, psoriasis or pityriasis amantiacea may appear similar. In the last of these conditions large numbers of thick scales are present around hairs. In alopecia areata where there arepatches of hair loss there is usually no scaling and small numbers of broken tapering hairs (exclamatory mark hairs) can be seen.

## Table5.11 Features of Tinea Capitis

| Organism | Hair invasion | Wood's light | Source | Common in |
|---|---|---|---|---|
| *M. canis* | Ectothrix | positive | cat, dog | Europe, cities |
| *M. audouinii* | Ectothrix | positive | Human | Africa |
| *M. ferrugineum* | Ectothrix | positive | Human | SE Asia |
| *T. violaceum* | Endothrix | negative | Human | India, Middle East, Africa |
| *T. tonsurans* | Endothrix | negative | Human | USA, Mexico |
| *T. soudanense* | Endothrix | negative | Human | Africa |
| *T. verrucosum* | Ectothrix | negative | Cattle | Europe |
| *T. schoenleinii* | Favic | yellow | Human | sporadic |

### 5.1.5. Tinea manuum

Dry-type dermatophytosis affecting the palms caused by *Trichophyton rubrum* may accompany foot infections. The palm is covered with fine scales and there may be involvement of the finger nails; itching is generally minimal. The involvement of one hand and both feet is typical and suggestive of this condition although bilateral palmar infections may also occur. Other dematophytes may affect the palm or dorsum of the hand, particularly if there is a disease of keratinization such as palmar/plantar keratoderma. This form of infection has to be distinguished from eczema and psoriasis.

**Table5.12 Hand Disease and Dermatophytosis**

| | **Dermatophytosis** | **Psoriasis** | **Hand eczema** |
|---|---|---|---|
| **Site** | may be unilateral | Bilateral | Bilateral |
| **Other sites** | Feet<br>Groin | Elbows<br>Scalp | anywhere |
| **Nails** | thick, broken<br>onycholysis | Pitted<br>Onycholysis | transverse ridges |
| **Itch** | Yes | usually not | Yes |

## 5.2. *Candida* Infections

Infections caused by yeasts of the genus *Candida*are common and although they most frequently affect the mucous membranes or skin they may also produce systemic infections. The principal pathogen is *Candida albicans* although other species, such as *Candida tropicalis, C.parapsilosis, C. krusei* and *C.glabrata* may also cause human infections. *C. albicans* forms filaments or hyphae during the process of tissue invasion. The disease caused by these fungi is called either candidosis or candidiasis.There are**two distinct forms of candidosis – superficial or deep**. Superficial candidosis principally affects the sites of carriage of the organism such as the mouth or the vagina; sometimes it affects the skin or the nails. Infections of the skin generally involve body fold areas.

*Candida* species are normal commensals in the mouth, gastrointestinal tract and vaginal mucosa. They are less commonly isolated from the skin. Superficial *Candida* infections may occur in any part of the world although there are some differences. Interdigital candidosis is more common in the tropics whereas onychomycosis without paronychia due to *Candida* is mainly seen in colder climates. Factors predisposing to candidiasis are shown in Table 5.3 and generally it is possible to find an underlying reason for infection. The most common exception is vaginal candidosis where most women with the infection have no detectable predisposition. Although it may affect all ages, infants and elderly are particularly susceptible to superficial candidosis and this probably reflects immaturity or senescence of immune responsiveness.

The process of infection by *Candida* starts with adherence of commensal organisms to mucosalcells or keratinocytes. Spread from other patients or sources

is not necessary as most infections are endogenous; the key event appears to be a change in the level of resistance in the host. Adherence probably involves the interaction of a fungal cell wall polysaccharide with a human receptor site on an epithelial cell. Adherence is a prerequisite for the germination of yeasts to produce germ tubes and hyphal elements which can penetrate tissue.

**Pathology**

In the early stages of *Candida* invasion the main changes are the infiltration of the epithelium by neutrophils with some hyper- and parakeratosis. There is an upper dermal infiltrate of lymphocytes and plasma cells. Dysplastic changes of the epithelium may develop in some chronic infections of the oral mucosa raising the possibility that persistent oral candidosis, either on its own or in combination with some other factor, such as smoking, may lead to the development of oral squamous carcinomas.

### 5.2.1. Candidosis of skin and flexures

*Candida* is an important cause of skin inflammation in intertriginous areas.It is also frequently isolated from intertrigo in the infra-mammary folds, axillae, and groin, where the presence of small "satellite" pustules around the edge of the characteristic glazed erythema of intertrigo should raise suspicion.

The skin can be indirectly involved in vaginal *Candida* infection when there is spread of infection to the vulva and perineum. In this case a prominent red rush in the groin and on the upper surface of the thighs may appear with satellite pustules and papules. The same can occur in other sites, such as under the breasts and in the umbilicus. In some cases there is no underlying skin abnormality although groin candidosis in males and females is more common in diabetics. Eczema or psoriasis affecting the skin flexures may be accompanied by secondary candidosis.

Skin can be affected by *Candida* infectionin the finger or toe web spaces. This type of **interdigital candidosis** is commonerin hot climates. It may be the commonest type of foot infection in army groups in the tropics. Lesions are with soggy looking skin which is superficially eroded. Between the toes *Candida* may be a secondary invader in a lesion primarily caused by a dermatophyte.

***Candida* infection** of the skin sometimes accompanies **nappy dermatitis in infants**. Nappy rush in infants is a form of irritant eczema which can be secondarily infected with, amongst other organisms, *C. albicans*. The presence of yeasts may be suspected by the appearance of satellite pustules and this is confirmed by culturing the organisms from swabs of the area.Generalized cutaneous candidosis is rarely seen in newly born infants where the mother has a vaginal Candida infection prior to delivery. The baby's skin is covered with multiple pustules against a background of erythema.

### 5.2.2. Oral andoropharyngeal candidosis

Oral candidosis or thrush is a common infection of the elderly, denture wearers, infants and the immunocompromised patient. It is the commonest infectious complication of AIDS. There are a number of different clinical types of oropharyngeal candidosis (see Table 5.13).

**Table 5.13 Clinical Types of Oropharyngeal Candidosis**

| *CLINICAL TYPES OF OROPHARYNGEAL CANDIDOSIS* |
|---|
| – **Acute oral candidosis** |
| – **Chronic oral candidosis** |
| – **Mediam rhomboid glossitis –** a form of localized candidosis on the dorsal surface of the tongue |
| – **Secondary candidosis –** secondary to some other abnormality such as oral ulcers |
| – **Angular cheilitis due to *Candida*** |
| – ***Candida*oesophagitis** |

These different forms are largely distinguished by their chronicity and clinical appearances and can be further subdivided.

**Acute pseudomembranous candidosis** present with white plaques on the epithelium which is inflamed. The scattered nature of these appearances is suggestive of the speckling on a thrush's breast. This may present as an acute infection in infants, the elderly or in patients who are immunocompromised such as those with AIDS. In the latter the condition is often persistent and refractory to therapy – **chronic pseudomembranous candidosis.**

In some patients plaques are not formed but the mucosal surface appears red and glazed**, acute erythematous candidosis** also known as acute atrophic oral candidosis. In patients presenting with inflammatory changes and oral discomfort associates with dentures, denture sore mouth, persistent erythema associated with *Candida* is a common feature – **chronic erythematous candidosis**. While this is related to the presence of *Candida*, treatment of the yeast alone will not control the condition and the addition of oral antiseptics is usually necessary, suggesting that oral bacteria may also play a role.

In smokers chronic candidosis may have additional features such as the appearance of a white plaque which cannot be detached on the tongue and other areas of the mouth – **chronic plaque-like candidosis** (C*andida*leikoplakia). Histologically it contains epithelial atypia and, in some patients, oral carcinomas have developed. A few patients with chronic oral Candida infection may develop a pebbly appearance on the mucosa, **chronic nodular candidosis.**

Any of the above changes can be accompanied by splitting at the corners of the mouth, **angular cheilitis,** which in these cases may be due to *Candida* infection. This is an important and common sign of candidosis and it can be spotted easily (see Table 5.14).

**Table5.14 Angular Cheilitis**

| Causes | Appearances |
|---|---|
| *Candida* | erythema, cracking, oral candidosios |
| *Staphylococcus aureus* | erythema, cracking, no oral candidosis, often eczema elsewhere |
| Avitaminosis | erythema, cracking no oral candidosis |

**NB**. Secondary candidosis may accompany angular cheilitis due to iron deficiency
**Median rhomboid glossitis** takes the form of a chronic lozenge shaped area of *Candida* infection on the dorsal surface of the tongue.
In most patients the main focus of infection is on the buccal mucosa, but in severely infected individuals there is involvement of the tongue or pharynx, as well as the oesophagus. Oesophageal candidosis is mainly seen in patients with AIDS, leukemia or chronic mucocutaneous candidosis. While it may present with retrosternal pain on swallowing it is often silent. Secondary oral infections due to *Candida* may occur in patients with epithelial abnormalities such as hyperkeratosis or ulceration in lichen planus, pemphigus and white sponge naevus.

## 5.2.3. Vaginal candidosis

Vaginal *Candida* infection is normally caused by *C. albicans* although other *Candida* species such as *C. glabrata* or *C. tropicalis* have also been cultured. It can occur in pregnant women or diabetics but one of the features of this condition is that there is usually no underlying abnormality to be found. Theories about the causes of vaginal candidosis abound from the use of tampons and tightly fitting underwear to immunological deficiencies. Generally, however, no consistent predisposing causes can be found and severely immunocompromised women do not usually show a higher frequency of persistent vaginal infection than appropriate control groups. The main clinical forms of vaginal candidosis are shown in Table 5.15.

**Table5.15Clinical Forms of Vaginal Candidosis**

| Clinical Forms of Vaginal Candidosis |
|---|
| – Acute (pseudomembranous or erythematous) vaginal candidosis |
| – Chronic relapsing vaginal candidosis |
| – Persistent vaginal candidosis |

The symptoms of all forms of candidosis are similar with the appearance of itching and discharge. Vaginal pain and dispareunia may also occur. The clinical appearances are varied but the main variations are presence or absence of soft white plaques (thrush). The course of infection is unpredictable and although most women have a single episode of infection others have either recurrent attacks or persistent thrush. No clear reasons for this have been found although those with

recurrent symptoms have been found to have a higher frequency of familiar atopoic diseases such as hay fever or asthma suggesting that sensitization might play a role in the development of symptoms. Women on high dose oestrogen replacement therapy may also have more frequent episodes of vaginal candidosis.
Secondary candidosis may occur in those with underlying mucosal disease such as pemphigoid, lichen planus or Bechcet's syndrome.

### 5.2.4. Chronic mucocutaneous candidosis

The rare syndrome of chronic mucocutaneous candidosis usually presents in childhood or infancy with oral, nail and cutaneous candidosis which recurs despite treatment. Other chronic skin infections such as warts (papilloma viruses) and dermatophytes may also appear. An adult form also exist. A classification of chronic mucocutaneous candidosis is shown in Table 5.16.

**Table 5.16 Classification of Chronic Mucocutaneous Candidosis (CMC)**

| Childhood onset | Adult onset |
|---|---|
| Inherited CMC – autosomal recessive type<br>Inherited CMC – autosomal dominant type<br>CMC associated with polyendocrinopathy (usually hypoparathyriodism, hypoadrenalism or hypothyroidism)<br>Idiopathic CMC | – CMC associated with thymoma<br>– CMC associated with systemic lupus erythematosus |

The oral lesions are usually of the chronic pseudomembranous type or plaque types. The skin may be covered with crusted plaques – the so called *Candida* granuloma- particularly where the infection has spread to the face or scalp. The finger nail changes affect the nail plates,nail folds and periungual skin, all of which may be severe dystrophic.
A large number of immunological abnormalities have been thought to be associated with this condition but with few exceptions these may alter over time and with therapy. For this reason it is likely that the real defect, or defects, in most patients with this condition remains unknown and the immunological investigation of children with this abnormality is not necessary unless they have very extensive infection or as history suggestive of abnormal responses to other infections, such as chicken pox or boils. Here it is with excluding functional leucocyte abnormalities such as chronic granulomatous disease although such patients usually have a history of internal infection. With the exception of bronchiectasis most patients with CMC do not have internal disease, although the severely affected patient may later develop systemic infection such as tuberculosis. A suggested plan of investigations in suspected cases of CMC is shown in Table 5.17.

**Table 5.17 Suggested Plan of Investigations in Suspected Cases of CMC**

| *Suggested plan of investigations in suspected cases of CMC* |
|---|
| – Genetic history (in CMC associated with polyendocrinopathy inheritance is also autosomal recessive<br>– Endocrine screen (thyroid, parathyroid, adrenal, autoantibodies)<br>– In severe cases immunological work up – T lymphocyte and phagocyte functional assays<br>– In adults – chest X-ray to exclude thymoma<br>– Many patients with CMC develop a spontaneous remission as they get older while others deteriorate. As there is a wide range of clinical expression in this syndrome all patients should be followed up closely. |

## 5.3. *Malassezia* Infections

***Malassezia*** (lipophilic) yeasts are skin-surface commensals which have also been associated with certain diseases, the commonest of which are pityriasis versicolor, *Malassezia* folliculitis, seborrhoeic dermatitis and dandruff. In addition, these organisms can rarely cause systemic infections, usually in neonatal infants receiving intravenous lipid infusions.

The taxonomy of the *Malassezia* (formerly *Pityrosporum*) yeasts is in the process of revision and they have been regrouped on the basis of DNA content.

Within the genus *Malassezia*, however, there are yeast with different shapes and site preferences on human skin. Some are round and are most common on the trunk; others are oval and are more common on the scalp. In addition, the formation of short stubby hyphae by round yeasts on the skin surface is a feature of the development of pityriasis versicolor and this form is described as *Malassezia furfur*. Occasionally oval yeasts without hyphae have been found to cause pityriasis versicolor.

### 5.3.1. Pityriasis versicolor

The pathogenesis of pityriasis versicolor is still ill-understood. The disease occurs in young adults and older individuals but is less common in childhood. Pityriasis versicolor is a common disease in the tropics and elsewhere in otherwise healthy patients, and there is no evidence of immunosuppression in these groups. However it has also been associated with Cushing's syndrome and immunosuppression associated with transplantation, but not with AIDS. The pigmentary changes which characterize this infection are thought to follow the inhibition of melanin formation by substances, such as azelaic acid, produced by yeasts enzyme activity.

The rush consists of multiple hypo- or hyperpigmented, occasionally red, macules which are distributed across the upper trunk and back; with time these coalesce. The lesions are asymptomatic and scaly. Patients usually notice this infection because of its unsightly appearance. In the tropics fear of other conditions such as leprosy may bring the patients to see a doctor.

Lesions can also be highlighted by shining a Wood's light on the area. They fluoresce with a yellowish light, although this is generally a weak response and complete darkness as well as powerful light source are necessary.

### 5.3.2. *Malassezia* folliculitis

A second condition associated with *Malassezia* yeasts is an itchy folliculitis on the back und upper trunk which often appears after a summer holiday and sun exposure. *Malassezia* folliculitis is a clinically distinct condition most often seen in teenagers or young adult males. Lesions are itchy papules and pustules which are often widely scattered on the shoulders and back. The condition has to be distinguished from acne as it does not respond to the same range of treatment (see Table 5.18).

**Table 5.18 Differential Diagnosisof *Malassezia* Folliculitis and Acne**

| | ***Malassezia* folliculitis** | **Acne vulgaris** |
|---|---|---|
| **Comedones** | No | Yes |
| **Itch** | Yes | Seldom |
| **Facial lesions**<br>**precipitated by sum exposure** | Rare<br><br>Common | Common<br><br>Uncommon |
| **Response to:**<br>**1) antibiotics**<br>**2) azoles** | <br>No<br>Yes | <br>Yes<br>No |

### 5.3.3. *Malassezia* yeasts and seborrhoeic dermatitis

Lipophilic yeasts of the genus *Malassezia* are part of the normal skin flora and therefore any evidence that they are either directly or indirectly implicated in the pathogenesis of common skin diseases such as dandruff or seborrhoeic dermatitis is difficult to assess. However:

– *Malassezia* yeasts are found in large quantities in the scales of seborrhoeic dermatitis and dandruff.

– Most patients with seborrhoeic dermatitis or dandruff respond to treatment with azole antifungal agents and this coincides with the disappearance of the yeasts.

– In animals it is possible to induce similar skin scaling by the application of *Malassezia* yeasts.

– Patients with seborrhoeic dermatitis have significantly raised levels of antibody to these organisms

Seborrhoeic dermatitis is one of the earliest and most consistent abnormalities seen in patients with AIDS but is also common in perfectly healthy individuals. The relationship between infantile seborrhoeic dermatitis and these organisms is less well established although heavy colonization with *Malassezia* has been documented in association with cradle cap eczema of the scalp.

The main clinical feature of seborrhoeic dermatitis is erythema together with greasy scales in the scalp, eyebrows and eye lashes, in the nasolabial folds, behind the ears and over the sternum.

## 5.4. Rarer Superficial Infections

**White piedra** is a chronic infection of the hair shaft caused by the yeast, *Trichosporom beigelii*. It is generally sporadic and rare and the infection is mainly seen in genital hair. It may also affect the axilla and scalp. The lesions are soft yellowish nodules around the hair shafts, trichomycosis axillaries where hairs in the axillae are covered with a soft yellowish coating is caused by a bacterial infection associated with sweating.
**Back piedra** caused by *Piedra hortae* is a rare infection confined to the tropics. Here scalp hairs are surrounded by a dense black concretion to produce a small nodule.
**Tinea nigra** is an infection of palmar or plantar skin caused by the black yeast, *Phaeoannelomyces werneckii*. It is mainly seen in the tropics but can present in Europe and the United States. The main differential diagnosis is an acral melanoma as it presents as a flat pigmented mark on the hands or feet. If the lesion is scraped with a glass slide it can be shown to be scaly. Lesions are usually solitary.
**Alternaria** species cause a rare form of skin granuloma often presenting with ulceration in normal or immunocompromised patients. The lesions are most often located over exposed sites such as the dorsum of the hands.
**Scopulariopsis brevicaulis** causes a form of onychomycosis and may occasionally be isolated from toe-web spaces. The onychomycosis is generally confined to the great toe nail which develops a light tan discoloration.
**Other fungi** may also be isolated from dystrophic nails. These include species of *Fusarium, Aspergillus* and *Pyrenochaet*. Generally they are secondary invaders of already dystrophic nails.

## 5.5. Deep Mycosesand the Skin

While the commonest fungal infections affecting the skin are those caused by superficial pathogens, mycoses affecting the subcutaneous tissue or those disseminated from deep foci, such as the lung, may also involve dermis and epidermis.

### 5.5.1. Subcutaneous Mycoses

The subcutaneous mycosis or mycoses of implantation may all affect the skin in the course of their evolution. In most cases they develop following traumatic injury and inoculation of the infective organisms. They are sporadic, mainly occur in the tropics and subtropics and chiefly affect manual workers.The main infections are:

– mycetoma
– chromoblasomycosis and pjaeohyphomycosis

– sporotrichosis
– rarer infections such as lobomycosis and subcutaneous zygomycosis.

### 5.5.1.1. Mycetoma (Madura foot)

Mycetoma is a chronic subcutaneous infection caused by fungi (eumycetoma) or filamentous bacteria, (actinomycetes, actinomycetoma). The characteristic of this infection is the formation of large granules or grains of filaments within abscesses. The latter drain through sinuses onto the skin or affect the bone causing chronic osteomyelitis. A key step in the diagnosis is to distinguish between fungal and actinomycete causes, as the latter are treatable with chemotherapy whereas the former generally require surgery. Patients usually come from the tropics. The features of mycetoma are summarized in Table 5.19.

**Table 5.19 Summary of the Features of Mycetoma**

| | |
|---|---|
| **Origin of patients** | Central and northern South America, Africa, Middle East, India and Pakistan |
| **Clinical features** | Chronically swollen limb with draining sinuses |
| **Symptoms** | Pain just before dermal abscess ruptures |
| **Characteristics** | Small but visible black, white or red grains in discharge from sinuses |
| **Tests** | Direct microscopy, histopathology, culture, X-ray (lytic bone lesions) |

Organisms causing mycetoma include
– **Fungi** – *Madurella mycetomatis* (black grains), *M.grisea* (black grains), Pseudallescheria boydii (white/yellow grains)
– Actinomycetes – *Actinomadura madurae* (white/yellow grains), *Streptomyces somaliensis* (white/yellow grains), *Nocardia* species (grains only visible with microscope).

### 5.5.1.2. Chromoblastomycosis (chromomycosis)

Chromoblastomycosis is a chronic infection affecting the dermis and the epidermis caused by pigmented or dematiaceous fungi. The characteristic feature is the presence of thick-walled, pigmented, rounded cells (muriform or sclerotic cells) in skin scrapings or biopsy material. It occurs as a rare, sporadic infection in humid parts of the tropics. The skin is involved by a verrucous lesion which spreads slowly on exposed sites such as the lower legs or hands. Occasionally lesions are flat, plaque-like and atrophic. The main organisms involved are *Fornasecaea pedrosoi, Cladosporium carrionii*, and *F. compacta*. The disease features are summarized in Table 5.20.

**Table 5.20 Summary of the Featues of Chromoblastomycosis**

| | |
|---|---|
| **Origin of patients** | Central and South America, Africa, South-East Asia, Japan |
| **Clinical features** | Warty growth or atrophic annular plaques |
| **Characteristics** | Pigmented muriform cells in skin scales or in biopsy |
| **Tests** | Direct microscopy, histopathology, culture |

Another infection caused by pigmented fungicalled **phaeohyphomycosis** presents a subcutaneous cyst. These are generally diagnosed after surgical excision and are found in certain numerous pigmented hyphae in an inflammatory cyst wall.

### 5.5.1.3. Sporotrichosis

Sporotrichosis is the infection caused by *Sporothrix schenckii*, a dimorphic fungus found in soil and plant debris. Infections occur over a wide geographic range in the tropics and subtropics including the United States. Although it most commonly presents as a skin infection – cutaneous sporotrichosis – systemic sporotrichosis – presenting with lung lesions or arthritis may also occur. The organism gains entry through traumatic injury. Infections occur sporadically, although certain occupational groups, such as those who handle plant materials or soil (gardeners, packers, florists) may be infected. The clinical lesions are of two types. Fixed lesions are solitary granulomas which ulcerate and are often confined to the face or exposed areas. They most resemble cutaneous leishmaniasis. Lymphangitic lesions spread along the course of lymphatics with the appearance of a chain of secondary nodules. These resemble either *Mycobacterium marinum* (fish-tank granuloma) infections or leishmaniasis. A summary of the features of sporotrichosis is given in Table 5.21.

**Table 5.21 Summary ofthe Features of Sporotrichosis**

| | |
|---|---|
| **Origin of patients** | USA and Central/South America, South Africa, Japan, Australia, rare in Europe |
| **Clinical features** | Fixed type – solitary granuloma/ulcer<br>Lymphangitic type – primary granuloma with secondary nodules along lymphatics |
| **Characteristics** | Few organisms on biopsy. Single fungal cell surrounded by eosinophilic “star” – asteroid body (haematoxylin/eosin stain) |
| **Tests** | Culture, histopathology |

**Other subcutaneous fungal infections** are rare. They include lobomycosis, a rare infection seen in Central and South America which resembles an inflammatory keloid scar. Cutaneous zygomycosis (phycomycosis) occurs on Africa or Latin America and presents with woody swelling of the faceor limbs.

Most subcutaneous mycoses are chronic infections and may present years after the patient hasleft an endemic area. They should, therefore, be considered as potential causes of illness in immigrants from tropical countries.

### 5.5.2. Systemic Mycoses

Systemic fungal infections sometimes present with skin lesions and, when this occurs, their recognition may simplify the diagnostic process. There are two main groups of fungi which cause systemic disease.
The **respiratory pathogens** include: *Histoplasma capsulatum* (histoplasmosis), *Histoplasmacapsulatum* var. *duboisii* (African histoplasmosis), *Coccidioides immitis* (coccidioicomycosis), *Blastomyces dermatitidis* (blastomycosis), and *Paraccoccidioides brasilienis* (paracoccidioidomycosis). Primary infection in all cases usually occurs in the lungs and the majority of patients inhaling the organisms manage to control the infection, the only evidence of exposure being a positive skin test. Alternatively the lesions may be walled-off in lung granulomas or produce chronic pulmonary infiltrates or cavitation; they may disseminate to other sites including the skin. This may occur rapidly with the eruption of multiple skin or mucous membrane lesions particularly in the immunocomprimised patient with defective T lymphocyte-mediated immunity. Features of the skin complications of these infections are shown in Table 5.22.

**Table5.22Features of the Skin Complications of Systemic Fungal Infections**

| Disease | Endemic area | Superficial lesion | Skin and underlying disease |
|---|---|---|---|
| Histoplasmosis | Worldwide not Europe | oral ulcers<br>skin papules, ulcers<br>erythema multiforme | chronic disseminated AIDS<br><br>acute pulmonary disease |
| African histoplasmosis | Africa | skin ulcers, abscesses, papules | disseminated |
| Coccidioidomycosis | USA<br>Central/South America | skin granulomas<br>erythema nodosum | disseminated<br>primary infection |
| Blastomycosis | USA, Canada, Africa | Plaques | disseminated |
| Paracocidioidomycosis | Central/South America | mucosal ulcers<br>papules | chronic disseminated<br>acute disseminated |
| Candidosis | Worldwide | folliculitis<br>nodules, abscesses | iv drug abusers<br>neutropenics |
| Aspergillosis | Worldwide | Abscesses | chronic granulomatous disease |
| Mucormycosis | Worldwide | skin necrosis | Burns |
| Fusarium | Worldwide | necrotic papules | neutropenia |
| Cryptococcosis | Worldwide | papules, ulcers, abscesses | AIDS, lymphoma, transplant patients |

Rarely direct inoculation of these organisms into the skin as a result of a laboratory accident may produce a local granuloma with peripheral lymphadenopathy which usually resolves without treatment.
The **systemic opportunistic fungal pathogens** such as *Aspergillus* enter via various routes from the lungs to the gastrointestinal tract. They less commonly disseminate to the skin; but they may involve this site in specific circumstances. Skin lesions occur in about 15% of cases of disseminated cryptococcosis caused by *Cryptococcus neoformans*, which is now an important systemic mycosis, occurring in between 3% and 13% of AIDS patients. Where appropriate, biopsy of a skin lesion may provide the diagnosis.

### 5.5.6. Use of the Laboratory

The laboratory diagnosis of fungal infections depends on four different approaches: direct microscopy, culture, serology and histopathology. For most superficial mycoses the first two are quite sufficient to establish the identity of the organism.

#### 5.5.6.1. Taking Specimens

For most skin lesions the edge or active margin is the site most likely to contain viable fungi. If the lesion is a blister, the roof will contain the fungal cells.
Appropriate material can be taken by scraping the lesion gently with a solid scalpel such as a banana-shaped scalpel, a disposable scalpel or even a glass slide. In any case care must be taken to avoid cutting into the skin; the object is to remove the easily detachable superficial scales.
Swabs from the mouth or vagina are taken directly from lesions and should be sent to the laboratory as soon as possible. Skin scales are best sent either in disposable packs or folded in dark paper. Dermatophytes will survive for several months in this material.
Specimens can be viewed directly by the clinician using a microscope. Material is mounted in 5-10% potassium hydroxide (KOH) which softens the keratinized cells. Generally the higher the concentration of KOH, the quicker the softening will be, although the stronger solutions are more caustic. For nails, material may take one hour to soften and the process can be hastened by gentle warming of the glass slide. Certain fungi such as *Malassezia* yeasts as well as some nail pathogens can be stained with a mixture of Parker ink and KOH (50:50), which colours these organisms blue. Other staining procedures are available such as Gram stains of smears and the use of calcoflour white, a fluorescent brightener which accentuates the fungal cell walls under fluorescent illumination. The nigrosin or India ink satins may also be applied to skin smears for *Cryptococcus* although this is designed principally for cerebrospinal fluid examination.
The use of direct microscopy can be practiced on the office or consulting room and can be applied to different materials from skin to sputum. One area of immediate use is, in the diagnosis of mycetomas, where a grain obtained by gently opening an

unruptured sinus with a sterile needle can be examined with KOH. If filaments can be distinguished under high-power magnification, the infection is fungal, whereas if they cannot be seen it is likely to be caused by an actinomycete.

### 5.5.6.2. Culture Techniques for Fungi

Generally, the methods used to culture fungi in the laboratory are simple; fungi are seldom fastidious organisms. The following points are worth remembering.
Failure to grow fungi is common with certain materials such as nail samples. This is probably due to the fact that fungi in the distal nail segment are not viable. Try to take material as near to the proximal edge of the nail as possible.
Most yeasts grow quickly – within two to four days – although *Cryptococcus* is often slower on primary isolates. Drematophyte identification is usually complete within fourteen days. However, more exotic fungi may have to be passed on to a reference laboratory. A delay in reporting the result does not necessarily mean that the specimen has been lost.
It is almost impossible to examine skin scales or recover fungi if they are heavily coated with medication. This should be removed with an alcohol swab before taking the skin scraping.
If a systemic pathogen is suspected, warn the laboratory. Some of these fungi (e.g. *Histoplasma capsulatum* and *Coccidioides immitis*) are potentially infectious to laboratory staff.

### 5.5.6.3. Serodiagnosis in Mycology

Serology, the detection of antibody responses, is helpful in some situations. Serology has no value for the diagnosis of superficial infections.

**Table 5.23 Use of Serodiagnosis in Mycology**

| Infection | Test and value |
|---|---|
| **Mycetoma** | Immunodiffusion – poor diagnostic use |
| **Histoplasmosis** | Immunodiffusion, complement fixation- useful |
| **Coccidioidomycosis** | Immunodiffusion, complement fixation- useful |
| **Cryptomycosis** | Latex agglutination for antigen – very useful |
| **Systemic candidosis** | Numerous tests, mainly of research use only |
| **Aspergillosis** | Numerous tests, poor results in immunodeficient |

### 5.5.6.4. Histopathology

The recognition of fungi in tissue is an important part of the diagnosis of fungal infections. Histopathology is not very useful in the diagnosis of superficial infections. Fungi generally stain poorly with hematoxylin and eosin satin and special stains, such as **periodic acid-Schiff** and **methenamine silver (Grocott)**, are used.The former stains fungal cell walls red/pink, the latter black. The

**mucicarmine** stain is specific for the cryptococcal capsule which it stains pink. A guide to recognition of some pathogens is given in Table 5.24.

**Table 5.24 Recognition of Pathogens**

| Description | Diagnosis |
|---|---|
| **Epidermis** | |
| Non-pigmented hyphae, no yeasts | Dermatophyte or *Hendersonula* |
| Pigmented hyphae | Tinea nigra |
| Yeasts, mycelium plus pseudomycelium | Candidosis |
| Yeasts, oval/round yeasts with/without short hyphae – cell wall thick at bud site | *Malassezia* |
| **Dermis** | |
| Yeasts with large capsule, pleomorphic | Cryptococcosis |
| Yeasts, mycelium plus pseudomycelium | Candidosis |
| Small oval yeasts, intracellular, no hyphae | Histoplasmosis |
| Large yeasts with broad base to buds | Blastomycosis |
| Large round structure (spherule) filled with endospores | Coccidioidomycosis |
| Large yeasts with multiple buds (cartwheel) | Paracoccidioidomycosis |
| Few pleomorphic yeasts – asteroid bodies | Sporotrichosis |
| Large amorphous structure with filaments up to 1-2 μm surrounded by neutrophils | Mycetoma |
| Pigmented thick walled rounded cells with septa, in dermis or epidermis | Cromoblastomycosis |

## 5.5.7. Therapy

The treatment of superficial fungal infections depends on three different approaches:

- The use of topical broad-spectrum substances analogues to antiseptics
- The removal of the site of the infection, the stratum corneum, with keratolytic compounds
- The use of specific antifungal drugs

### 5.5.7.1. Antifungal Antiseptics

Most of these compounds fall into one or two groups. The first are dyes with weak antifungal activity, such as gentian violet or brilliant green. Castellani's paint which contains magenta and resorcinol is a further example. The second group contains substances such as 2% selenium sulphide and 20% sodium hyposulphite, both of which are used in the treatment of pityriasis versicolor.

All these compounds are cheap but can be messy to apply and are generally slower in action than specific antifungal drugs. Selenium sulphide is also an irritant and can stain the skin.

### 5.5.7.2. Keratolytics

The keratolytics work by removing the stratum corneum, the principal site of the fungal infection in superficial mycoses. The best-known example is salicylic acid. The combination of 3% salicylic acid and 6% benzoic acid to form Whitfield's ointment is a useful preparation which is effective against dermatophytes. It is a potential irritant and in sensitive areas such as the groin should be used as a half strength preparation. One of the disadvantages of Whitfield's ointment is that it is thick and sticky to apply, although there is at least one version available in some parts of the world where the combination is formulated in a cream base.

### 5.5.7.3. Antifungal Compounds

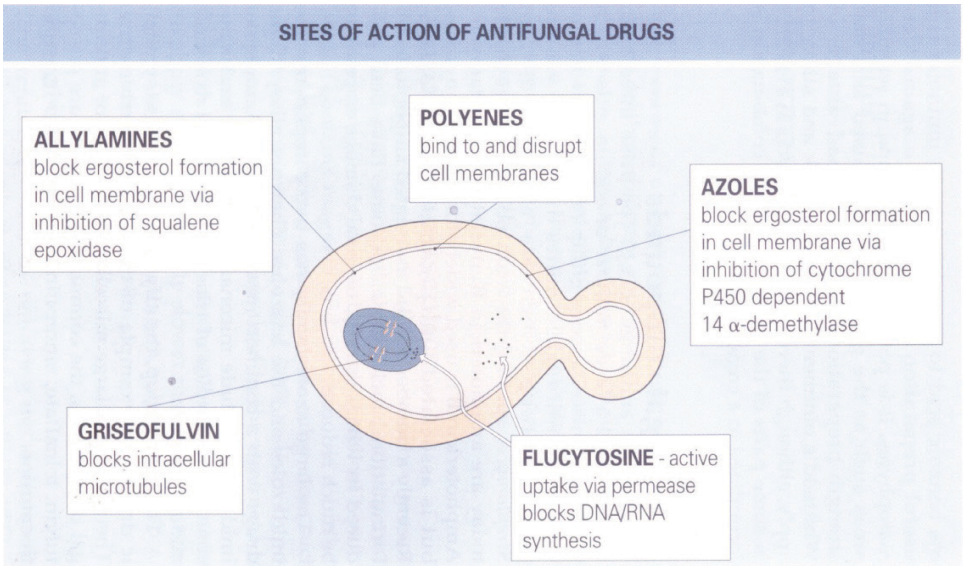
The modern antifungal drugs comprise three main families and a large number of compounds which make up a miscellaneous group of drugs. The first of the major antifungal families discovered was the **polyene** group which are all derived from *Streptomyces* species; the main polyene drugs in use today are amphotericin B, nystatin and natamycin. Amphotericin B is used widely for systemic mycoses, but is associated with significant renal toxicity. Recently a number of lipid associated amphotericin B formulations, including a liposome, have been produced in which the risk of renal damage appears to be much reduced.

The large **azole** family has two components: the imidazoles amd the triazoles. They are all synthetic drugs with a common mode of action. Examples of imidazoles include miconazole, econazole and ketokonazole; examples of triazoles include itraconazole and fluconazole.

The third group,the **allylamines**, are also synthetic drugs. An example of this group is terbinafine. There is also a large miscellaneous group of antifungal compounds, the commonest of which are griseofulvin, tolnaftat, amorolfine, cyclopiroxolamine and flucytosine.

The modes of action of these drugs are different (see Fig. 5.2). Most affect the integrity of the cell membrane. Antifungals which block other processes include flucytosine (RNA and DNA synthesis) and nikkimycins and echinocandins (cell wall synthesis). Most antifungal drugs, in laboratory tests, are inhibitory to the growth of fungi (fungistatic) at concentrations achievable at the sites of infection whereas a few are able to destroy the organisms (fungicidal). The difference may be important clinically where host resistance is impaired or otherwise ineffective. Antifungal compounds than inhibit fungicidal action may also cure infection with shorter courses of drug therapy than those required for fungistatic compounds. The uses of various antifungal drugs are shown in Table 5.25.

## Fig 5.1 The modes of action of polyenes, azoles, allylamines and griseofulvin




## Table 5.25 The Uses of Various Antifungal Drugs

| **Drug** | **Fungal affected** | **Formulation (dose)** | **Side effects** |
|---|---|---|---|
| Aphotericin | *Candida,* most systemic | topical, iv | iv: pyrexia, malaise, renal failure, anemia |
| Nystatin | *Candida* | Topical | skin staining |
| Natamycin | *Candida,* Dermatophyte | Topical | - |
| Clotrimazole | most superficial | Topical | -* |
| Miconazole | most, not *Aspergilli* | topical,iv | iv: tachycardia, anaphylaxis* |
| Econazole | most superficial | Topical | -* |
| Ketoconazole | most superficial, some systemic, not *Aspergilli* | topical, oral | oral: hepatitis*, androgen blockade, nausea |
| Fluconazole | most superficial/systemic not *Aspergilli* | oral, iv | nausea |
| Intraconazole | most superficial/systemic | Oral | nausea |
| Griseofulvin | dermatophytes | Oral | nausea, headache, photosensitivity |
| Terbinafine | dermatophytes, sporotrichosis<br>dermatophytes<br>*Candida*<br>*Malassezia* | Oral<br><br><br>topical | nausea, abdominal pain<br><br><br>- |
| Flycytosine | *Candida*<br>*Cryptococcus* | oral, iv | agranulocytosis, resistance |
| Amorolfine | most superficial | Topical | - |
| Tolnaftate | dermatophytes | Topical | - |
| Cyclopiroxolamine | most superficial | Topical | - |
| * *most topical azole antifungals may occasionally cause allergic contact dermatitis* | | | |

### 5.5.7.4. The Management of Specific Fungal Diseases of the Skin

#### 5.5.7.4.1. Dermatophytosis

***Topical therapy***

The simple principle of the therapy is that if theinfection is not widespread or involves hair or nails, topical therapy is generally used. For most superficial infections caused by dernatophytes a topical imidazole, tolnaftate, terbinafine, amorolfine or cyclopiroxolamine is adequate.

The minimum treatment period has never been clearly established. Generally, the specific antifungal agents clear tinea cruris/corporis within two weeks; Whitfield's ointment takes about four weeks. Terbinafine is effective after seven day's therapy and there is evidence that even shorter period of one or two days may be effective in many patients.

In tinea pedis of the dry type, most topical agents take four weeks to produce a remission and the relapse rate is high. Topical therapy is not indicated for treatment of scalp infections; in nail disease there is some evidence that some topical agents, such as tioconazole, amorolfime and cycloporoxolamine, may produce recoveries although success rates are comparatively low.

***Oral Therapy***

**Griseofulvin** is used for dermatophytosis of the skin, dry-type infections, and scalp and nail disease. The dose of griseofulvin is 10 mg/kg daily. For certain scalp infections, such as those caused by *Microsporum canis*, griseofulvin is an appropriate therapy. It should be given for at least six weeks in tinea capitis.

Long-term success rates in onychomycosis affecting the toe nails are less than 40% after twelve months of therapy, although the results in finger nail infections are considerably better. In the treatment of the nail disease and dry-type *Trichophyton rubrum* infections, remission rates are lower than with oral azoles, ketoconazole and intraconazole, or terbinafine.

**Ketoconazole** is helpful in dermatophytosis. However, in view of the rare complication of hepatitis in 1:10.000 cases it has largely been superseded by itraconazole even though the main risk of this complication followed long-term therapy for nail disease.

**Fluconazole** is available in a few countries for the treatment of dermatophytosis in doses of 50-100 mg daily. The use of intermittent doses of 150-300 mg weekly is under investigation for the treatment of onychhomycosis.

**Itraconazole** is given in doses of 100 mg daily for tinea cruris/corporis (two weeks) and tinea pedis (four weeks). At higher doses shorter periods of treatment appear to be effective, e.g. 400 mg daily for one week in tinea pedis (dry type). In nail disease a treatment regimen of 200 mg daily for three months is used. An alternative regimen of 400 mg daily for one week of each month for two months (finger nails) or three months (toe nails) is under evaluation.

**Terfinafine** is used in doses of 250 mg daily for a wide range of dermatophyte infections. Oral terbinafine produces better results than griseofulvin in the

treatment of nail disease where the optimum time for therapy is about three months for toe-nail infection and six weeks for finger-nail infection. For tinea cruris/corporis and dry-type foot infections it is given orally for two weeks. Shorter treatment periods are also under evaluation, such as 250 mg daily for tinea corporis. In addition it is available for use in children with dermatophytosis at doses of 62.5 mg (for children under 20 kg) and 125 mg (20-40 kg). This includes tinea capitis where four weeks therapy is as effective as six weeks of griseofulvin. One feature of this drug, which is fungicidal, is the very low relapse rate at long-term assessment (e.g. six months) after therapy.

**5.5.7.4.2. Candidosis**

Most superficial *Candida* infections respond to topical nystatin, azoles, terbinafine or amorolfine. In oral infections topically applied nystatin lozenges or suspension and amphotericin B lozenges are useful for uncomplicated infections, although the taste of the medication is bitter. Micomazole oral gel is better tolerated by infants. When treating patients with oral candidosis associated with dentures, these should be removed overnight and cleaned with saline or a disinfectant before they are replaced. For infection in the immunocompromised it is often necessary to use an orally absorbed drug, such as ketoconazole, fluconazole or itraconazole. In AIDS patients the dose of itraconazole (200 mg) and ketoconazole (400 mg) is double of that normally used as absorption may be impaired. If possible, treatment is stopped in AIDS patients after achieving remission and recurrences are retreated as necessary. Continuous therapy is best avoided.

For vaginal infections, topically applied azoles are available, usually in tablet form, for single-dose vaginal use, for example clotrimazole, sulconazole, econazole and miconazole. Longer topical regimens can also be used. Where topical therapy is unacceptable, oral therapy with a single dose of fluconazole 150 mg or itraconazole 400 mg given in one day can be used. There is no magic answer to **chronic or relapsing vaginal candidosis.** In all cases it is important to confirm that the recurrence of symptoms really is accompanied by the presence of *Candida*. Longer-term therapy with a course of oral fluconazole or itraconazole over two to three weeks followed by topical therapy with clotrimazole or even betadine once or twice weekly over three months may occasionally bring halt to repeated episodes of infection.

For paronychia, topical azoles are helpful if applied in **solution** from and over three to four months or until the nail fold becomes less swollen. Similar results can be obtained with oral azoles, such as ketoconazole or itraconazole. The latter are the only effective therapies for genuine nail-plate invasion due to *Candida.*

In the rare cases of chronic mucocutaneous candidosis, remission should be induced using ketoconazole, fluconazole or itraconazole. If possible it is best to treat relapses when they occur by using intermittent azole therapy for three or seven days if there is a severe clinical relapse.

Resistance to ketoconazole and fluconazole has been described where the drug has been given for a period of several months in the face of continuing infection. This

appears to be a problem where either drug has been given for long periods in patients with immunological deficiencies such as AIDS or chronic mucocutaneous candidosis.

#### 5.5.7.4.3. Pityriasis versicolor

Pityriasis versicolor responds well to selenium sulphide given for at least two weeks, most topical azoles, amorolfine or topical terbinafine for one or two weeks, and oral ketoconazole (400 mg as a single dose, or five days of 200 mg daily). Itraconazole (200 mg for seven days) is also effective, ketoconazole shampoo is effective if given for two to three application only. There are three potential problems in the management of this infection

– Relapse occurs very frequently particularly in patients living in the tropics
– Patients often believe that they are still infected because the skin discoloration takes several months to revert to normal. They need to be reassured that this is the normal course and that they do not need more treatment.
– Because of the thickness of the *Malassezia* cell wall, organisms persist on the skin surface for up to four weeks after the yeasts have been killed. Direct microscopy of the skin is a poor guide in the early phases to successful treatment.

### 5.5.7.4. *Malassezia* folliculitis

*Malassezia* folliculitis is difficult to treat. Oral ketoconazole or ketoconazole shampoo are the most effective approaches although itraconazole is an alternative (seven to ten days). Unfortunately topical therapies seldom work well.

### 5.5.7.4. Seborrhoeic dermatitis

While conventional therapy with low-to-medium strength topical corticosteroids or tar-based preparations may be helpful, most patients with seborrhoeic dermatitis respond well to topical azolesor terbinafine or oral azole therapy. The combination of an azole with hydrocortisone may be helpful. Relapse is frequent whatever the therapy used. Treatments for specific superficial mycosis are summarized in Table 5.26.

**Table 5.26 Treatments Commonly Used for Specific Superficial Mycoses**

| **Dermatophytosis** (wide range of choice but not nystatin) | |
|---|---|
| Interdigital tinea pedis | most topical antifungals; azoles and allyaminesare probably faster than rest |
| Dry-type tinea pedis | usually oral antifungal:<br>terbinafine (2 weeks),<br>itraconazole (4weeks),<br>griseofulvin (4-8 weeks) |
| Tinea corporis, minor infections | as with interdigital tinea pedis |
| Tinea corporis, extensive infections | terbinafine, itraconazole (2-3 weeks);<br>griseofulvin (4-12 weeks) |
| Tinea capitis | griseofulvin (10-15 mg/kg daily) for at least 6 weeks; in some countries, terbinafine 125 mg |

| | |
|---|---|
| | daily for 4 weeks |
| Tinea cruris | topical antifungals, griseofulvin, terbinafine, itraconazole (2 weeks) |
| Onychomycosis | terbinafine, griseofulvin, itraconazole; topicals are usually less active – tioconazole, amorolfine |
| **Candidosis** | |
| Cutaneous candidosis | topical nystatin, azoles, terbinafine, amorolfine |
| Vaginal candidosis | single-or multiple-dose topical azole pessaries or vaginal tablets; in severe infections – fluconazole, itraconazole |
| Oral candidosis | topical nystatin, amphotericin B, miconazole; in severe infections – fluconazole, ketyoconazole. itraconazole |
| Pityriasis versicolor | topical ketoconazole shampoo, other azole creams, terbinafine, selenium sulphide; in severe infections – oral itraconazole/ketoconazole |

### 5.5.7.4. Subcutaneous mycoses

**Mycetoma–eumycetoma:** Only infections due to *Madurella mycetomatis* respond in about 50% of cases to ketoconazole 200 mg daily. For other cases a trial of chemotherapy with griseofulvin or itraconazole can be givem but usually radical surgical removal is the only alternate. In these circumstances it may be preferable to do nothing unless the lesion is very large or painful.

**Mycetoma-actinomycetoma:** Therapy with a sulphonamide, dapsone (100 mg daily) or cotrimoxazole is useful. In extensive cases, rifampicim or streptomycin may have to be used as well; alternatives include amikacin and imipenem.

**Chromomycosis:** itraconazole 100 mg daily sometimes with flucytosin 30-35 mg/kg qid for a patient with normal renal function is effective. Alternatives include amphotericin B plus flucytosine on its own, thiabendazole and the application of heat.

**Sporotrichosis:** potassium iodide in saturated solution of 1 ml ds increased dropwise per dose to 406 ml tds is the standard approach. If the dose is increased too rapidly patients may develop severe nausea and salivation due to iodism. The drug may be given in milk. Alternatives include itraconazole in a dose of 100 mg daily and terbinafine in a dose of 250 mg daily. Treatment takes at least six weeks but the length of therapy should be guided by clinical response.

### 5.5.7.4 Systemic mycoses

Considering the therapy of systemic fungal infections there are some general principles which should be understood.

– For most systemic mycoses, particularly those in severely ill patients, intravenous amphotericin B still remains the therapy of choice in doses of 0.6 – 1.0 mg/kg daily.

– Fluconazole (oral or intravenous) is used for some forms of systemic candidosis, such as peritonitis, systemic candidosis in the non-neutropenic and

oropharyngeal candidosis. It can be used for cryptococcal meningitis in the AIDS patient, either as the primary therapy or as a continuous suppression after remission to prevent relapse. It can also be used for cutaneous cryptococcosis where there is no evidence of deep infection.
– Itraconazole (oral) is an alternative drug in histoplasmosis, blastomycosis and some forms of cryptococcosis. It is also used for certain *Aspergillus* infections, such as those occurring in the transplant patient.
– New developments include liposomal and lipid complexed forms of amphotericin B, which at present are reserved for severely ill neutropenic patients or those who have failed on other therapies. Also terbinafine is being investigated in some forms of systemic mycosis, such as aspergillosis.

## 5.8. Onychomycosis

### 5.8.1. Definition and Prevalence

Onychomycosis is one of the commonest dermatological conditions.Recent mycological surveys indicate its prevalence between 7% and 10% both in Europe and the USA. Onycomycosis is an infection of the nail apparatus by fungi that include dermatophytes, nondermatopyte moulds and yeasts (mainly *Candida* species). The toenails are affected in 80% of all cases of onychomycosis; dermatopyte infection, mostly due to *Trichophyron rubrum*, is the cause in over 90% of cases.
Onychomycoses are classidied clinically as
– distal and lateral subungual onychomycosis (DLSO),
– superficial white onychomycosis (SWO),
– proximal subungual onychomycosis (PSO),
– candidal onychomycosis and
– total distrophic onychomycosis (TDO)

### 5.8.2. Distal and Lateral Subungual Onycomycosis

Distal and lateral subungual onycomycosis (DLSO) accounts for the majority of cases and is almost always due to dermatophyte infection. It affects the hyponychium, often at the lateral edges initially, and spreads proximally along the nail bed resulting in subungual hyperkeratosis and onycholysis although the nail plate is not initially affected. DLSO may be confined to one side of the nail or spread sideways to involve the whole of the nail bed, and progresses relentlessly until it reaches the posterior nail fold. Eventually the nail plate becomes friable and may break up, often due to trauma, although nail destruction may be related to invasion of the plate by dermatophytes that have keratolytic properties. Examination of the surrounding skin will nearly always reveal evidence of tinea pedis. Toenail infection is an almost inevitable precursor of fingernail dermatophytosis, which has a similar clinical appearance although nail thickening is not as common.

### 5.8.3. Superficial White Onychomycosis

Superficial white onychomycosis (SWO) is also nearly always due to a dermatophyte infection, most commonly *T. mentagrophytes*.
It is much less common than DLSO and affects the surface of the nail plate rather than the nail bed. Discoloration is white rather than cream and the surface of the nail plate is noticeably flacky. Onycholysis is not a common feature of SWO and intercurrent foot infection is not as frequent as in DSLO.

### 5.8.4. Proximal Subungual Onychomycosis

Proximal subungual onychomycosis (PSO)without evidence of paronychia is an uncommon variety of dermatopyte infection often related to intercurrent disease. Immunosuppressed patients, notably those who are human immunodeficiency virus-positive, may present with this variety of dermatophyte infection; conditions such as peripheral vascular disease and diabetes also may present in this way. Evidence of intercurrent disease should therefore be considered in a patient with PSO.

### 5.8.5. Candidal Onychomycosis

Infection of the nail apparatus with *Candida* yeasts may present in one of four ways: (I) chronic paronychia with secondary nail dystrophy; (II) distal nail infection; (III) chronic mucocutaneous candidiasis; and (IV) secondary candidiasis. Chronic paronychia of the fingernails generally occurs in patients with wet occupations. Swelling of the posterior nail fold occurs secondarily to chronic immersion in water or possibly due to allergic reactions to some foods, and the cuticle becomes detached from the nail plate thus losing its water tight properties. Microorganisms, both yeasts and bacteria, enter the subcuticular space causing further swelling of the posterior nail fold and further cuticular detachment, i.e. a vicious circle. Infection and inflammation of the area of the nail matrix eventually lead to a proximal nail dystrophy.
Distal nail infection with *Candida* yeasts is uncommon and virtually all patients have Raynaud's phenomenon or some other form of vascular insufficiency. It is unclear whether the underlying vascular problem gives rise to onycholysis as the initial event or whether yeast infection causes the onycholysis. Although candidal onychomycosis cannot be clinically differentiated from DLSO with certainty, the absence of toenail involvement and typically a lesser degree of subungual hyperkeratosis are helpful diagnostic features.
Chronic mucocutaneous candidiasis has multifactorial etiology leading to diminished cell-mediated immunity. Clinical signs vary with the severity of immunosuppression, but in more severe cases gross thickening of the nails occurs, amounting to *Candida* granuloma. The mucous membranes are almost always involved in such cases.

Secondary candidal onychomycosis occurs in other diseases of the nail apparatus, most notably psoriasis.

### 5.8.6. Total Dystrophic Onychomycosis

Any of the above varieties of onychomycosis may eventually progress to total nail dystrophy where the nail plate is almost completely destroyed.

### 5.8.7. Diagnosis

Although 50% of all cases of nail dystrophy are fungal in origin it is not always possible to identify such cases accurately. Treatment needs to be administered long-term and enough time must elapse for the nail to grow out completely before such treatment can be designated as successful. Toenails take around 12 months to grow out and fingernails about 6 months. This is far too long to await the results of therapeutic trial and, in any case, treatment is not always successful. If the diagnosis is not confirmed, and improvement does not occur, it is impossible to tell whether this represents treatment failure or an initial incorrect diagnosis. Although the cost of diagnostic tests may be deemed high at times of budgetary constraint, the cost is always small relative to inappropriate and unnecessary treatment.

Laboratory diagnosis consists of microscopy to visualize fungal elements in the nail sample and culture to identify the species concerned. The success or otherwise of such tests depends upon the quality of the sample, the experience of the microscopist and the ability of the laboratory to discriminate between organisms that are likely pathogens, organisms growing on the nail as saprophytes, and contamination of the culture plate.

Given that dermatophyte onychomycosis is primarily a disease of the nail bed rather than of the nail plate, subungual debris taken from the most proximal part of the infection is likely to yield the best results. In DSLO material can be obtained from beneath the nail: a small dental scraper is most useful for this purpose. If the nail is onycholytic, then this can be cut back and material can be scraped off the underside of the nail as well as from the bed. As much material as possible should be submitted to the laboratory because of the relative paucity of fungal elements within the specimen. In SWO, the surface of the infected nail plate can be scraped and material examined directly. PSO is rare and again should be scraped with a scalpel blade. However, punch biopsy to obtain a sample of the full thickness of nail together with the nail bed may be necessary. Some of the material obtained is placed on a glass slide and 20% potassium hydroxide added. Fifteen to 20 minutes should be allowed to elapse before examining the sample by direct microscopy. The addition of Parker's blue/black ink may enhance the visualization of the hyphae. An inexperienced observer may very well misdiagnose cell walls as hyphae and care should be taken to examine all of the specimens as fungal elements within the material may be very scanty.

The remaining material should be cultured on Saboraud's glucose agar, usually with the addition of an antibiotic. The culture plate is incubated at 28°C or at least 3 weeks before it is declared negative, as dermatophytes tend to grow slowly.
Direct microscopy can be carried out by the clinician. However, nail microscopy is difficult and should only be carried out by those who do it on a regular basis. Fungal culture should always be carried out in a laboratory experienced in handling mycology specimens, because of potential pitfalls in interpretation of cultures. It must be remembered that the most common cause of treatment failure is incorrect diagnosis, which is usually made on clinical grounds alone. This should not be further compounded by incorrect laboratory interpretation of results.
Histology is almost never required and its use is usually confined to other causes of nail dystrophy. Such dystrophies, notably psoriasis, regularly yield *Candida* yeasts on culture but they are rarely casual in etiology of fungal nail infection.

### 5.8.8. Reasons for Treatment

Although dermatophyte onychomycosis is relentlessly progressive there remains a view among some practitioners that it is a trivial cosmetic problem that does not merit treatment. In the elderly the disease can give rise to complications such as cellulites and therefore further compromise the limb in those with diabetes or peripheral vascular disease. While these complications may not be common they are certainly serious. The high prevalence of the disease is the result of heavy contamination of communal bathing places by infected users; disinfecting the floors of such facilities is very difficult because fungal elements are protected in small pieces of keratin. It is therefore logical to try to reduce the number of infected users by effective treatment and thus reduce the disease prevalence. Finally, onychomycosis is a surprisingly significant cause of medical consultation and of absence from work.
Onychomycosis should not therefore be considered a trivial disease, and there is a sound case for treatment on the grounds of complications, public health considerations and effects on the quality of life.

### 5.8.9. Treatment

Both topical and oral agents are available for the treatment of fungal nail infection. The primary aim of treatment is to eradicate the organism as demonstrated by microscopy and culture. Clinical improvement and clinical cure are secondary end-points based on a strict scoring system of clinical abnormalities in the nail apparatus. It must be recognized that successful eradication of the fungus does not always render the nails normal as they may have been dystrophic prior to infection. Such dystrophy may be due to trauma or non-fungal nail disease; this is particularly likely in cases where yeasts or non-dermatophyte moulds (secondary pathogens and saprophytes respectively) are isolated.
Invariably mycological cure rates are about 30% better than clinical cure rates which are often below 50%. This suggests that eradication of the organism does

restore the nail to its previous state prior to infection even though that state may not be completely ”normal” as defined by a scoring system.
Systemic therapy is almost always more successful than topical treatment, which should only be used in SWO, possibly very early DSLO or when systemic therapy is contraindicated.

### 5.8.9.1. Topical therapy

There are several topical antifungal preparations available both as prescription-only medicines and on an over-the-counter basis. The active antifungal agent in these preparations is an imidazole, an allylamine or a polyene, or a preparation that contains a chemical with antifungal, antiseptic and sometimes keratolytic properties such as benzoic acid, benzoyl peroxide, salicylic acid or an undecenoate. Products that are specifically indicated for nail infection are available as a paint or lacquer that is applied topically.
There are no published studies on the efficacy of salicylic acid and methyl undecenoate in fungal nail infection and their use cannot be recommended.
Amorolfine nail lacquer has been shown to be effective in around 50% of cases of both fingernail and toenail; infection where only cases with infections of the distal portion of the nail were treated. While it is clearly possible to achieve clinical and mycological cure with topical nail preparations, these cure rates do not compare favourably with those obtained with systemic drugs. Currently, topical therapy can only be recommended for the treatment of SWO where the infection is confined to the distal edge of the nail.
A combination of topical and systemic therapy may improve cure rates still further or possibly shorten the duration of therapy with the systemic agent.
Although there are no studies comparing one topical preparation with another in a properly controlled fashion, it is likely that amorolfine nail lacquer is the most effective preparation of those available.

### 5.8.9.2. Systemic therapy

The three drugs currently listed for general use in onychomycosis are listed in Table 5.27.

**Table5.27 Systemic Agents for Onychomycosis with Major Advantages, and Strength of Recommendation and Quality of Evidence Grading**

| Drug | Advantages | Disadvantages | Main drug interactions |
|---|---|---|---|
| Griseofulvin | Licensed in both adults and children, inexpensive, extensive experience | Lengthy treatment necessary in both fingernail and toenail infection: poor cure rates; high relapse rates; no pediatric formulation currently available: | Warfarin, cyclosporine, oral contraceptive pills |

| | | | |
|---|---|---|---|
| | | contraindicated in lupus erythematosus, porphyria and severe liver disease | |
| Terbinafine* | Fungicidal: high cure rates (compared with griseofulvin); good compliance | No suspension formulation: idiosyncratic liver and skin reactions; reversible taste disturbance in 1:400 patients | Plasma concentrations reduced by rifampicin, increased by cimetidine |
| Intraconazole | Active against *Candida albicans:* pulse treatment regimens are possible | Less effective in dermatophyte onychomycosis than terbinafine; monitoring of liver function required for treatment durations of longer than 1 month; contraindicated for children under 12 years of age and in pregnancy | Enhanced toxicity of anticoagulants (warfarin), anti-histamines (terfenadine and astemizole), antipsychotics (sertindole), anxiolytics (midazolam), digoxin, cisapride, cyclosporine and simvastadin (increased risk of myopathy); reduced efficacy of itraconazole with concomitant use of H2 blockers, phenytoin and rifampicin |

*Terbinafine has better cure rate and lower relapses rate than intraconazole for dermatophytes

### *Griseofulvin*

Griseofulvin is weakly fungistatic, and acts by inhibiting nucleic acid synthesis, arresting cell division and inhibiting cell wall synthesis. It is available in tablet form and is licensed for use in children with onychomycosis at a recommended dose for age group of 1 month and above of 10 mg/KG daily. It requires to be taken with fatty food to increase absorption and aid bioavailability. In adults the recommended dose is 500 mg daily given for 6-9 months in fingernail infection and 12-18 months in toenail infection. Mycological cure rates in fingernail infection are reasonably satisfactory at around 70% but griseofulvin is a disappointing in toenail disease where cure rates of only 30-40% can be expected.

It is generally recognized than 500 mg daily is too small a dose for nail infection and 1 g daily is most often prescribed, but there is no evidence that this improves cure rates in toenail infection. Although the cost of griseofulvin is very low, its poor cure rate, often necessitating further treatment, suggests that its cost/efficacy ratio is relatively high. Both direct and historical comparison with studies of the newer antifungal agents terbinafine and itraconazole suggest that griseofulvin is no longer the treatment of choice for dermatophyte onychomycosis.

Side effects include nausea and rashes in 8-15% of patients. In adults, it is contraindicated in pregnancy and the manufacturers caution against men fathering a child for 6 months after therapy.

***Terbinafine***

Terbinafine, an allyamine, inhibits the enzyme squalene epoxidase thus blocking the conversion of squalene epoxide in the biosynthetic pathway of ergosterol, an integral component of the fungal cell wall. Its action results in both a depletion of ergosterol, which has a fungistatic effect, together with an accumulation of squalene, which appears to be directly fungicidal. The minimum inhibitory concentration (MIC) of terbinafine is very low, approximately 0.004 μg $mL^{-1.}$. This is equivalent to the minimal fungicidal concentration (MFC), demonstrating that this drug is truly fungicidal *in vitro*. It is the most effective currently available antidermatophyte agent *in vitro* and clinical studies strongly suggest that this is also the case *in vivo*.

***Itraconazole***

Itraconazole is active against a range of fungi including yeasts, dermatophytes and some non-dermatopyte moulds. It is not as active in *vitro* against dermatophytes as terbinafine, its MIC being 10 times greater. Although it is generally felt to be a fungistatic agent it can achieve fungicidal concentrations, although its MFC is about 10 times higher than its MIC.

Both terbinafine and itraconazole persist in the nail for a considerable period and elimination follows from the plasma. This property has given rise to a novel intermittent ("pulsed") treatment regimen using itraconazole in nail infection.

***Terbinafine vs. itraconazolein dermatophyte onychomycosis.*** Both of these drugs have been shown to be more effective than griseofulvinin dermatophyte onychomycosis and therefore the optimum choice of treatment lies between terbinafine and itraconazole.

Terbinafine is licensed at a dose of 250 mg daily for 6 weeks and 12 weeks in fingernail and toenail infection, respectively. Itraconazole is licensed at a dose of 200 mg daily for 12 weeks continuously or alternatively at a dose of 400 mg daily for 1 week per month. It is recommended that two of these weekly courses, 21 days apart, are given for fingernail infections and three courses for toenail disease.

**Treatment of yeast infections**

Most yeast infections can be treated topically, particularly those associated with paronychia. Antiseptics can be applied to the proximal part of the nail and allowed to wash beneath the cuticle, thus sterilizing the subcuticular space. Ideally, such antiseptics should be broad spectrum, colourless and non-sensitizing. An imidazole lotion alternative with antibacterial lotion is usually effective.

Itraconazole is the most effective agent for the treatment of candidal onychomycosis where the nail plate is invaded by the organism. It is used in the same dosage regimen as for dermatophytes, i.e. 400 mg daily for 1 week per month repeated 2 months in fingernail infection. *Candida* infection of toenails is much less common but can be treated as above using three or four pulses.

**Treatment of non-dermatophyte moulds**

Many varieties of saprophytic moulds can invade diseased nail. *Scopulariopsis brevicaulis* is the commonest of these and may be a secondary pathogen. Its response to systemic antifungal agents is variable, although terbinafine is probably the drug of choice in that the primary nail disease is quite likely to be a dermatophyte infection that is masked by the *Scopulariopsis*. There is little categorical evidence to support the choice of one drug. In the USA and Europe cyclopriox nail laquer has its advocates. Nail avulsion followed by an oral agent during the period of regrowth is probably the best method of restoring the nail to normal.

### 8.9.3. Treatment failure

Although terbinafine is demonstrably the most effective agent in dermatophyte onychomycosis a consistent failure rate of 20-30% is found in all studies. If the most obvious causes of treatment failure, notably poor compliance, poor absorption, immunosuppression, dermatophyte resistance and zero nail growth are excluded, the commonest cause of failure is likely to be kinetic. Subungual dermatophytoma has been described and it is likely that this tightly packed mass of fungus prevents penetration of the drug in adequate concentrations. In such cases partial nail removal is indicated. It is best demonstrated that cure rates of close to 100% can always be achieved if all affected nails are avulsed under ring block prior to commencement of treatment. However, this is neither feasible, nor necessary in most cases and the best approach is to try to identify those individual nails that are likely to fail and to remove the offending area.

Reports of long-term follow-up of treated patients have recently been presented, suggesting that positive mycology at 12 and 24 weeks after commencement of therapy are poor prognostic signs and may indicate a need for retreatment or for a change of drug. However, this work remains to be confirmed.

Cure rates, both short- and long-term, may be influenced by correction of associated orthopedic and podiatric factors to avoid, as much as possible, trauma that particularly affects the great toenails.

# VI. INFLAMMATORY DERMATOSES

## 6.1. Ezematous Inflammation and Its Stages

**Eczema** asa clinical descriptive term describes a proress that is clearly superficial in form and that, early, is erythematous, papulo-vesicular, oozing and crusting and, late, red-purple, scaly, lichenified and possibly pigmented. Epithelial disruption and non-sharp margination are its characteristics.
Eczema can be defined histologically by the presence of a predominantly lymphohistiocytic infiltrate around the upper dermal blood vessels, associated with varying degrees of spongiosis and acanthosis.
The terms *eczema* and *dermatitis* are regarded as synonymous.

**Table 6.1 Stages of Eczematous Inflammation**

| Stage | Morphology of Lesions | Symptoms | Examples | Treatment |
|---|---|---|---|---|
| Acute | Vesicles, blisters, intense red | Intense itch, stinging, burning | Acute contact dermatitis, acute nummular eczema, stasis dermatitis, pompholyx | Cold wet compresses, steroid, antihistamine, antibiotics |
| Subacute | Red, scale, fissuring, parched appearance, scalded appearance | Slight to moderate itch, stinging, burning | Contact allergy, irritation, atopic dermatitis, stasis dermatitis, nummular eczema, asteatotic eczema | Topical steroid, emollients, antihistamine, antibiotics |
| Chronic | Thickened skin, lichenified excoriation, fissuring | Moderate to intense itch | Atopic dermatitis, lichen simplex chronicus, fingertip eczema, hyperkeratotic eczema | Topical steroid, antihistamine, antibiotics, emollients |

## 6.2. Dyshidrotic Eczema

**Background:** Dyshidrotic eczema is a recurrent or chronic relapsing form of vesicular palmoplantar dermatitis of unknown etiology. Dyshidrotic eczema also is termed pompholyx, which derives from *cheiropompholyx*, which means "hand and bubble" in Greek.
The etiology of dyshidrotic eczema is unresolved and believed to be multifactorial. It is considered a reaction pattern caused by various endogenous conditions and exogenous factors.
**Pathophysiology:** Several hypotheses exist for the pathophysiology of dyshidrotic eczema. The original hypothesis of sweat gland dysfunction is not valid, since vesicular lesions are not associated with sweat ducts. Patients usually do not have

hyperhidrosis. Dyshidrotic eczema may be associated with atopy. Of patients with dyshidrosis, one half have atopic dermatitis. Exogenous factors (e.g. contact dermatitis to nickel, balsam, cobalt; sensitivity to ingested metals; dermatophyte infection; bacterial infection) may trigger episodes. These antigens may act as haptens with a specific affinity for palmoplantar proteins of the stratum lucidum of the epidermis. The binding of these haptens to tissue receptor sites may initiate pompholyx. Emotional stress and environmental factors (e.g. seasonal changes, hot or cold temperatures, and humidity) reportedly exacerbate dyshidrosis.

Controversy exists concerning whether a distant fungal infection can cause palmar pompholyx as an "id reaction". The finding that one third of pompholyx occurrences on the palms resolve after treatment for tinea pedis supports this hypothesis.

**Causes:** The cause of dyshidrotic eczema is unknown. The condition often appears related to other skin diseases (e.g. atopic dermatitis, contact dermatitis, allergy to ingested metals, dermatophyte infection, bacterial infection, environmental or emotional stress). Several factors may participate in causing dyshidrotic eczema and pompholyx.

Atopy: As many as 50% of patients with dyshidrotic eczema have reportedly had personal or familial atopic diathesis (eczema, asthma, hayfever, allergic sinusitis). Serum immunoglobulin E (IgE) level frequently is increased, even in patients who do not report a personal or familial history of atopy. Occasionally, dyshidrotic eczema is the first manifestation of atopic diathesis. Nickel sensitivity: this may be a significant factor in dyshidrotic eczema.

Low-nickel diets: these have reportedly decreased the frequency and severity of pompholyx flares. A high palmoplantar perspiration rate has been suggested to result in a local concentration of metal salts that may provoke the vesicular reaction.Contact allergy has been documented in 30% of patients with dyshidrotic eczema.“Id”- reaction: dyshidrotic eczema outbreaks are not always associated with exposure to sensitizing chemicals or metals. Controversy surrounds the possible existence of an “id- reaction”, which is a distant dermatophyte infection (tinea pedis, kerion of scalp) triggering a palmar pompholyx reaction (also termed pompholyx dermatophytid).

Fungal infection: pompholyx occasionally resolves when a tinea pedis infection is treated, then relapses when the fungal infection recurs, supporting the existence of this reaction pattern. Of patients who have a vesicular reaction to intradermal trichophyton testing, fewer than one third have experienced a resolution of pompholyx after treatment with antifungal agents.

Emotional stress: this is a possible factor in dyshidrotic eczema. Many patients report recurrences of pompholyx during stressful periods. Improvement of dyshidrotic eczema using biofeedback techniques for stress reduction supports this hypothesis.

Other factors: isolated reports of other possible causative factors exist, such as aspirin ingestion, oral contraceptives, cigarette smoking, and implanted metals.

**Age:** Dyshidrotic eczema affects individuals aged 4-76 years; mean age is 38 years. After middle age, the frequency of episodes tends to decrease.
**History:** Patients complain of pruritus of hands and feet with sudden onset of blisters. Burning pain or pruritus occasionally may be experienced before blisters appear. Episodes vary in frequency from once per month to once per year. Patients may report a variety of factors that possibly are related to eruptions:
Emotional stress
Personal or familial atopic diathesis (e.g. asthma, hay fever, sinusitis)
Certain work exposures (e.g. cobalt) and/or recreational exposures
Recent exposure to contact allergens (e.g., nickel, balsams, paraphenylenediamine, chromate, sesquiterpene lactones) before condition flares
Exposure to contact irritants before condition flares
Recent exposure to costume jewelry (patients with palmar pompholyx and allergic to nickel)
Recent treatment with intravenous immunoglobulin therapy
**Physical:** Symmetric crops of clear vesicles and/or bullae on the palms and lateral aspects of fingers characterize dyshidrotic eczema. Feet, soles, and the lateral aspects of toes also may be affected.In mildly affected patients, vesicles are present only on the lateral aspects of fingers and, occasionally, involve feet and toes.Vesicles are deep seated with a tapioca-like appearance, without surrounding erythema.May become large, form bullae, and become confluent. Typically resolve without rupturing, followed by desquamation. Hands are involved solely in 80% of patients, feet solely in 10%, and both hands and feet are involved in 10% of patients.With long-standing disease, patients' fingernails may reveal dystrophic changes (e.g. irregular transverse ridging, pitting, thickening, discoloration).Interdigital maceration and desquamation of the interdigital spaces often are present, despite the possible absence of a dermatophyte infection.Vesicles and/or bullae may become infected secondarily, and pustular lesions may be present. Cellulitis and lymphangitis may develop.
**Complications.** Secondary bacterial infection of vesicles or bullae can result in cellulitis, lymphangitis, and septicemia (rare).Dystrophic nail changes may develop with transverse ridging, thickening, discoloration, and pitting of nails.
**Lab Studies.** Diagnosis usually is made clinically. Bacterial culture and sensitivity exclude secondary infection. Blood tests usually are not ordered; however, IgE commonly is elevated. Use patch testing to exclude allergic contact dermatitis.
**Procedures.** Perform potassium hydroxide wet mount preparation to exclude dermatophyte infection.Punch biopsy for hematoxylin and eosin staining usually is not necessary. Punch biopsy for periodic acid-Schiff staining may help exclude dermatophytosis in patients with unresponsive disease.Use punch biopsy for direct immunofluorescence to exclude bullous pemphigoid.
**Histologic Findings:** Spongiosis with an epidermal lymphocytic infiltrate and intraepidermal vesicles or bullae are not associated with sweat glands.
**Medical Care:** Some mildly affected patients experience spontaneous resolution within 2-3 weeks. Biofeedback therapy for stress reduction has succeeded in some

patients. Outpatient care is multifaceted. The following treatment is appropriate if bullae are present. Use compresses with Burow solution (10% aluminum acetate). Apply in a 1:40 dilution bid/tid until bullae resolve (usually, within a few days). Drain large bullae with a sterile syringe, and leave the roof intact. Prescribe systemic antibiotics that cover *Staphylococcus aureus* and group A streptococci.Topical corticosteroids are the mainstay of treatment. Prescribe class I steroids bid/tid for up to 2 weeks, then class II or III steroids. Ointments penetrate skin better than creams; patients may prefer creams during the day. Topical antipruritics with pramoxine are useful.

Prescribe systemic corticosteroids. Prescribe either oral prednisone or intramuscular (IM) betamethasone sodium phosphate and betamethasone acetate suspension for severe episodes. Tapering of prednisone can follow IM treatment. IM triamcinolone acetonide (Kenalog) may be administered; its anti-inflammatory activity lasts 4-6 weeks.

For severe refractory pompholyx, prescribe azathioprine. Azathioprine has been used in refractory disease.

Consider measuring thiopurine methyltransferase levels, which may help guide azathioprine therapy.

Methotrexate at low doses and cyclosporine also have been successful in case reports.

Hand and/or foot UV-A therapy (alone or with oral or topical psoralen) improves the eruption and pruritus when administered 2-3 times per week. The dose typically starts at 0.5 J per treatment and is increased by 0.5 J at every other or every third treatment.

Nickel chelators, such as disulfiram (Antabuse), occasionally are used in nickel-sensitive patients who demonstrate a positive oral provocation test.

**Diet.**For nickel-sensitive patients, consider a low-nickel diet for 3-4 weeks. The diet regimen only rarely is successful and is difficult for patients to follow.The diet requires avoiding foods rich in nickel, such as canned foods, foods cooked in nickel-plated utensils, herring, oysters, asparagus, beans, mushrooms, onions, corn, spinach, tomatoes, peas, whole grain flour, pears, rhubarb, tea, cocoa, chocolate, and baking powder.For cobalt-sensitive patients, consider a low-cobalt diet that avoids apricots, beans, beer, beets, cabbage, cloves, cocoa, chocolate, coffee, liver, nuts, scallops, tea, and whole grain flour.

**Prevention.** Advise patients to avoid known contact irritants or allergens. Advise patients to reduce stress (may help some patients). Advise patients to follow a hand care regimen. Advise regular prophylactic use of emollients.

**Prognosis:** dyshidrotic eczema follows a chronic intermittent course. Fewer episodes occur after middle age.

## 6.3. Nummular Dermatitis

**Synonyms and related keywords:** discoid eczema, nummular eczema

**Background:** Nummular (meaning coin-like) dermatitis is an idiopathic disease that manifests as discrete round plaques. These plaques can be dry or exudative. It is a chronic condition with relapse and recurrence often at the same sites. Lesions wax and wane with changes in environmental conditions; it worsens in the winter, in low relative humidity, and in the presence of heaters. Nummular dermatitis is usually diagnosed clinically, and it is distinguished from generalized patchy dermatitis, which has ill-defined borders.

**Causes.**The etiology has not been clearly elucidated, but it appears to be multifactorial.Local trauma, irritating conditions, and venous stasis may play a role in the pathogenesis. Xerosis may also play a role. Venous insufficiency (and varicosities) may be related to involvement in affected lower extremities.Autoeczematization (lesional spread from the initial focal site) may account for multiple plaques.Lymphocytes are predominately $CD8^+$ in the epidermis and $CD4^+$ in the dermis. Mast cell–derived interleukin 4 (IL-4) appears to be involved in activation of the T- lymphocytes.

**Age.**The incidence peaks in the sixth and seventh decades. Another common population who may have nummular dermatitis is persons with atopic dermatitis who are in their second and third decades. Nummular dermatitis is rare in children.

**History.**Plaques may develop central clearing that resembles tinea corporis, which tends to be less vesicular, has a narrower border, and is duller in color.Contact dermatitis may have a pattern that approximates the way the offending agent came in contact with the skin, such as a linear pattern. It may become chronic in the setting of repeated exposure, such as with chromate and formaldehyde. The patient may recall contact to an allergen, such as poison ivy.

Psoriasis is often found on the extensor surfaces, especially at the joints, and it may have larger plaques, it is scalier, and it has a less pronounced irritation.

Lichen simplex chronicus often occurs on the lower legs, the neck, the scalp, or the scrotum; it is lichenified (thickened by chronic scratching) and does not have a clear border.

Stasis dermatitis may occur simultaneously on the lower extremities, and venous stasis may lead to the concomitant development of both conditions.

**Physical:** Diagnosis is usually based on the characteristic clinical appearance; a biopsy sample typically reveals a spongiotic reactive pattern.

Distinguishing between forms of dermatitis (e.g. xerotic eczema, atopic dermatitis, and nummular dermatitis) may be difficult, but, fortunately, it is not necessary to make proper treatment decisions. Lesions begin as papules or vesicles that coalesce to form confluent plaques with an erythematous base.Early lesions may be exudative and crusted, and, because of the moist environment, the lesions often become colonized by staphylococci and it increases the severity and the duration of the lesion.Secondary frank infection may occur, necessitating systemic antibiotics.

Late lesions are dry, scaly, and often excoriated secondary to moderate pruritus.Patients may report a burning sensation. The lower extremities and the dorsum of the hands are the most frequently affected areas, though the arms, the trunk, and the thighs may also be affected.Irritant hand dermatitis may present as a nummular pattern. Plaques may be single or multiple; symmetric bilateral involvement may occur.

**Lab Studies:** Tinea corporis should be excluded by scraping and microscopic analysis of a potassium hydroxide (KOH) preparation.

**Procedures:** A skin biopsy may be performed. While nonspecific, excluding other papulosquamous diseases listed in the differential diagnosis may be useful.

**Histologic Findings:** Biopsy findings mirror the evolution of the lesion. In the early stages, a nonspecific infiltrate is present with spongiosis, vesicles, and a predominant lymphocytic infiltrate. Eosinophils may be observed in the papillary dermis. Chronic lesions demonstrate epidermal hyperplasia, hyperkeratosis, and a pronounced granular cell layer. The papillary dermis may be fibrotic, with a perivenular infiltrate of lymphocytes and monocytes.

**Medical Care.**Emollients and topical class I-III topical steroids may be used. Bed rest and isolation from stress-provoking stimuli may be beneficial.Oral or parenteral steroids may be used as a temporizing measure in severe flares, followed by topical therapy.Oral antibiotics, such as dicloxacillin, cephalexin, or erythromycin, should be used in cases of secondary infection.A potent-to-intermediate potency steroid may be applied sparingly 2-4 times daily to the affected areas. Once lesions improve, a lower potency steroid is prescribed to avoid skin atrophy. Usually, a more effective treatment is a combination of a topical antibiotic and a steroid ointment applied twice daily. This therapy decreases inflammation and colonization by staphylococci. Nighttime pruritus may be treated with sedating oral antihistamines.

**Activity.**Activities that lead to perspiration and increased skin temperature may be irritating.Heat, drying conditions, and irritating activities should be avoided. Sunlight may be beneficial.

**Chronic disease.**Chronic lesions may be treated with tar ointments in addition to steroids, although patients may be resistant to this therapy because it is time consuming and messy.

**Severe disease.**Severe or generalized flares may be treated with tap water–moistened dressings on top of the steroid ointment. Oral or parenteral steroids may be used as a temporizing measure in severe flares, followed by topical therapy. Oral antibiotics, such as dicloxacillin, cephalexin, or erythromycin, should be used in cases of secondary infection.

**Prevention.**Temperature and humidity extremes can worsen lesions. Bathing is permissible, but hot water should be avoided. Patients should use mild, nondrying cleansers. Patients should be encouraged to use non-soap cleansers only for control of body odor and cleanliness (e.g. on the groin, axillae, and feet).Oil additives may be used in bathing water.To avoid drying of the lesions, an emollient should be used immediately after bathing.The skin may be patted dry, and the emollient

should be applied before the skin dries out completely.Creams are better emollients than lotions and should be encouraged. Clothing should be loose to avoid overheating, and irritating fibers, such as wool, should be avoided.A room humidifier is useful particularly when a heater or air conditioning is used.
**Prognosis:** Inform patients that the lesions tend to be persistent, are difficult to treat, and can reoccur in the same location.

## 6.4. Vesicular Palmoplantar Eczema

**Synonyms and related keywords:** pompholyx, dyshidrotic eczema, vesicobullous dermatitis, dyshidrosis, chronic relapsing vesiculosquamous eczema

**Background:** Vesicular palmoplantar eczema is a term used to describe a group of diseases characterized by vesiculobullous eruption involving mainly the hands and feet. Clinical presentations vary from acute explosive dermatitis to more chronic relapsing and remitting disease patterns. Although considerable overlap exists in the various forms of vesicular palmoplantar eczema, the disease can be divided into 4 distinct categories: pompholyx, subacute or chronic relapsing vesiculosquamous eczema, chronic vesiculohyperkeratotic or hyperkeratotic eczema, and "id- reactions".
**Pompholyx** may be further subdivided into vesicular and bullous forms in which patients present with acute eruptions of blisters over their palms and soles. **Chronic vesiculosquamous eczema**, also called dyshidrotic eczema, was initially thought to be caused by abnormal function of the sweat glands. This association has since been disproved, but the term dyshidrotic eczema is still used. Patients with this variant present with vesicles involving the inner sides of the fingers. The **chronic hyperkeratotic variety** involves mainly the central palms, where it causes thickening and fissures. This category is notoriously the most difficult to treat. An **"id-reaction"** refers to vesicular eruption of the hands, caused by a distal focus of infection, with fungal infections being the most common. Despite the wide range of clinical presentations, all 4 types are histologically characterized by features of dermatitis, such as spongiosis and exocytosis.
**Causes:** The etiology of hand eczema is unknown, but most observers suggest that intrinsic changes in the skin are responsible for this condition. However, several exogenous factors have been implicated in the causation of the disease. Coexisting atopy is common in patients with palmoplantar eczema. This is by no means the only causal relationship because many patients have no history of atopy.Emotional stress may also trigger episodes. Seasonal changes seem to be directly related to relapses, as episodes are most common in the spring and summer months. Warm weather has been known to initiate episodes.Although dysfunction of the sweat glands is no longer accepted as the cause of dyshidrotic eczema, increased sweating seems to exacerbate the condition. Photosensitivity to ultraviolet A (UVA)-1 has been reported as an etiologic factor in a small subset of patients with eczema. Therefore, worsening of the disease in summer months may be due to the

increase in exposure to sunlight. UVA-therapy is a widely accepted form of treatment for palmoplantar eczema. Sensitivity to certain metals, particularly nickel, has been linked to the condition. Other exogenous factors include balsams and various allergens in general. Drugs responsible for inducing episodes include oral contraceptive pills and aspirin. Palmoplantar eczema occurring after intravenous immunoglobulin therapy is reported. Bacterial infections play a role in both causation and in secondarily infecting lesions. Fungal infections are most commonly implicated in "id-reactions". Cigarette smoking may reduce the efficacy of topical therapy with psoralen and UVA (PUVA).

**Pathophysiology.**Vesicular palmoplantar eczema is often thought to have an unidentified intrinsic cause. Although many etiologic factors are described, the underlying pathology is unknown. Similarly, though certain triggers have been associated with the development or worsening of symptoms, how these triggers cause flares has not been elucidated.

The disease results in histologic evidence of dermatitis, such as spongiosis, which is often accompanied by lymphocytic infiltrates.

**Age.**Pompholyx most commonly occurs in patients aged 20-40 years, but it may occur in individuals of any age. Onset in patients younger than 10 years is unusual. The frequency of recurrent episodes of pompholyx decreases after middle age, though this is not true of chronic vesicular and hyperkeratotic variants.

**History:** The severity of symptoms varies, ranging from mild discomfort to acute severe episodes. Patients rarely require hospitalization. Itching, burning, and prickling sensations of the palms and soles precede the eruption of vesicles.Thereafter, small (1- to 2-mm) vesicles form, most commonly on the lateral sides of the fingers. In pompholyx, the central areas of the palms and soles may or may not be involved.Large vesicles can develop on the palms and soles and may coalesce to form confluent bullae.The lesions last for 2-3 weeks, after which spontaneous resolution generally occurs. Occasionally, large bullae may need to be aspirated. This phase is followed by desquamation.Palmoplantar eczema typically recurs, and episodes are more frequent during the spring and summer than in the fall and winter.The chronic hyperkeratotic variety results in severe itching accompanied by thickening and fissuring of the palm. This effect may decrease the mobility of the affected hand.

**Physical:** Clinical signs depend on the stage of disease. An absence of erythema is often an important clinical feature in the acute and chronic forms. Acute episodes are characterized by a sudden onset of small, clear vesicles or bullae that are said to be sago-like or tapioca-like in appearance.Vesicles and/or bullae are accompanied by severe, occasionally painful pruritus.Small vesicles may enlarge or become more confluent and present as large bullae (especially on the palms and soles).Vesicles and bullae subsequently dry out and resolve, usually without rupturing.In most individuals, desquamation occurs 2-3 weeks after the onset of vesicles and bullae.In some patients, a milder recurrence follows the initial severe episode. Secondary infections, such as impetigo, cellulitis or lymphangitis, are possible in patients with recurrent hand eczema.Secondary nail changes

(e.g.dystrophic nails, irregular transverse ridging, pitting, thickening, discoloration) can also occur.Subacute vesicular eczema tends to have a chronic relapsing course with more vesiculation and more erythema in the acute phases than in later phases.Residual erythema or some dryness or scaling occurs in the less-active phases. Fissures are common and painful sequelae. A form of microvesicular palmar eczema also occurs in association with dry nummular (discoid) eczema.Hyperkeratotic palmar eczema is characterized by highly itchy, hyperkeratotic palms. Fissures in the folds of the hands and fingers are common and painful. Fissures can limit the use of the hands.Typically, chronic eczema affects the central area of the palm or the palmar aspect of the hands and fingers.Only occasionally are vesicles visible on clinical examination, but spongiosis is found on histology.When they occur on the hands, id reactions typically involve the lateral sides of the fingers. These reactions often resolve when the primary infection is treated.

**Lab Studies.**The diagnosis of palmoplantar eczema is essentially a clinical one, and laboratory tests are not routinely performed. However, laboratory studies may be helpful in excluding other disorders.Elevated serum immunoglobulin E levels or positive results on prick tests may suggest an atopic tendency. Skin scrapings can indicate the presence of a fungus. Skin swabs may exclude bacterial infection.

**Procedures.**Perform patch tests to exclude contact dermatitis or a systemic reaction to contact allergen.Perform biopsy to distinguish eczema from psoriasis or some forms of palmoplantar hyperkeratoses.

**Histologic Findings:** Histologic features vary according to the stage of the evolution of disease. Usually, evidence suggests intracellular edema or spongiosis, lymphocytic infiltration of the epidermis, and intraepidermal vesicles or bullae in acutely affected persons. In chronically affected persons, spongiosis is present and often associated with epithelial proliferation and/or hyperkeratosis or psoriasiform epidermal hyperplasia. Dermis is often edematous, with a mixed perivascular inflammatory cell infiltrate.

**Medical Care:** Several modalities of therapy are available for the treatment and control of palmoplantar eczema. Therapy should be chosen according to the type and severity of the condition. Whenever possible, eliminate known triggers. If pruritus is a problem, antihistamines (e.g. hydroxyzine) can relieve some symptoms.

***Topical therapy*** includes high-potency glucocorticoids, Burow solution (aluminum acetate 1%, or potassium permanganate solution (1:8000 dilution), tacrolimus, and/or PUVA. Topical high-potency glucocorticoids, such as betamethasone valerate and clobetasol propionate are first-line of therapies. Application of these medications under plastic and vinyl occlusion enhances their efficacy. However, this method may predispose the patient to secondary bacterial infection; therefore, it should be used only intermittently and in the absence of coexisting infection. Acute, severe episodes of pompholyx benefit from rest, and bland applications with wet soaks and compresses and with drying agents such as Burow solution. Occasionally, large blisters may need to be aspirated. Newer agents, such as topical

tacrolimus, are just as effective at mometasone furoate in the treatment of chronic relapsing eczema of the hands. These topical immunosuppressants may be used as steroid-sparing agents to treat resistant palmar eczema, with minimal systemic absorption or effect. Use of other agents should be considered when plantar eczema is being treated, as this therapy is less effective on the soles of the feet than on the hands.

***Systemic therapy*** includes steroids, immunosuppressive agents (eg, azathioprine, cyclosporine), retinoids (including acitretin), and/or PUVA. Consider the use of systemic glucocorticoids or intralesional steroids in acute episodes when local therapy fails. These agents are not helpful for long-term treatment because of a potential for severe adverse effects. Cyclosporine, mycophenolate mofetil, and methotrexate either alone or in combination with steroids may be used for severe, recalcitrant cases. These agents have also been tried as steroid-sparing agents in chronic relapsing eczema. For hyperkeratotic eczema, consider the use of aromatic retinoids, such as acitretin, which help control hyperkeratosis. These agents are best used in relatively low doses because of adverse effects. Therapy may need to be continued indefinitely in cases of hyperkeratotic eczema and is often accompanied by topical occlusive therapy, with combined or alternating steroids and keratolytics (5-20% salicylic acid) or tar preparations.

***Other treatment options*** include treatment with intradermal injections of botulinum toxin A, X-ray therapy, and disulfiram (Antabuse).

**Prevention.** Elimination of known exacerbating factors, though often difficult to accomplish, is crucial in preventing relapses.Patients with established nickel sensitivity may benefit from nickel-free diets.

## 6.5. Asteatotic Eczema

**Synonyms and related keywords:** asteatotic dermatitis, eczema craquelé, eczema craquelatum, xerotic eczema, winter itch, etat craquelé

**Background:** First described by Brocq in 1907, using the term eczema craquelé, asteatotic dermatitis is characterized by pruritic, dry, cracked, and polygonally fissured skin with irregular scaling. It most commonly occurs on the shins of elderly patients, but it may occur on the hands and the trunk. In 1971, Domonkos described the appearance of this dermatitis as cracked porcelain. The pattern of cracking has been likened to a crazy pavement pattern. In 1999, Fitzpatrick likened asteatotic eczema to a dried-up riverbed. According to Caplan, superficial bleeding and fissures can occur as the epidermis loses water, as it splits, and as it cracks deeply enough to disrupt papillary dermal capillaries. The inflammation can be associated with asymmetric leg edema. Eczema with increased lichenification occasionally supervenes as patients rub and scratch the pruritic areas. The eruption can be generalized or localized. Generalized asteatosis is a distinct entity and

should provoke a search for possible associated diseases. Guillet divides the localized forms into 4 types:

– Asteatotic eczema of the lower extremities in elderly persons secondary to aging, dehydrated skin, and malnutrition
– Cracked erythema secondary to irritant contact dermatitis from soaps or detergents
– Eczema craquelé in areas in which corticosteroid therapy was discontinued
– Asteatotic eczema in neurologic disorders

**Pathophysiology:** Initially, excess water loss from the epidermis results in dehydration of the stratum corneum with upward curling of corneocytes. The outer keratin layers require 10-20% water concentration to maintain their integrity. A significant decrease in free fatty acids in the stratum corneum is present in people with asteatotic dermatitis. Stratum corneum lipids act as water modulators, and cutaneous loss of these lipids can increase transepidermal water loss to 75 times that of healthy skin. Elderly persons with decreased sebaceous and sweat gland activity, patients on antiandrogen therapy, people using degreasing agents, and people bathing without replacing natural skin emollients lost to bath water are at risk for asteatotic eczema.

When the stratum corneum loses water, the cells shrink. A significantly decreased cellular volume can stress the skin's elasticity, creating fissures. Edema in the dermis leads to additional stretch on the overlying epidermis. Fissures rupture dermal capillaries, causing clinical bleeding. The disruption of cutaneous integrity can result in inflammation with risk of infection. Transepidermal absorption of allergens and irritants is increased as the epidermis is damaged, increasing susceptibility to allergic contact dermatitis and irritant contact dermatitis. Allergic contact dermatitis and irritant contact dermatitis may cause a persistent and possibly more extensive dermatitis despite therapy. Furthermore, low environmental humidity contributes to xerosis, creating a clinical picture of asteatotic dermatitis in some dermatologic conditions, such as atopic dermatitis.

**Causes.**Multiple etiologic factors may coexist to cause asteatotic dermatitis, including the following:

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|---|
| • Xerosis and friction |
| • Frequent or prolonged bathing in hot water, use of soap on the involved site, and infrequent use of emollients for water retention in the stratum corneum |
| • Degreasing agents (Solvents, Cleansers) |
| • Decreased sebaceous and sweat gland activity in elderly persons |
| • Decreased keratin synthesis in elderly persons |
| • Low environmental humidity and cold winds that increase the loss of water by convection |
| • Radiation |
| • Long-term malabsorption of essential fatty acids, including linoleic acid and linolenic acid |
| • Nutritional deficiencies (Zinc deficiency; Essential fatty acid deficiency, such as linoleic acid deficiency or linolenic acid deficiency) |
| • Atopy |
| • Ichthyosis |
| • Thyroid disease - Myxedema and other thyroid diseases with diminished sweat and sebaceous |

gland activity
• Neurologic disorders - Decreased sweating in denervated areas
• Drugs - antiandrogen therapy and diuretic therapy
•Malignancies - malignant lymphoma, gastric adenocarcinoma, glucagonoma, angioimmunoblastic lymphadenopathy, breast cancer, large-cell lung carcinoma, and colorectal carcinoma

**Age.**The median patient age at presentation is 69 years. Asteatosis can also occur in young people.

**History.**During the winter months, an elderly person classically presents with pruritic and dry skin with dermatitis on the pretibial areas. Sometimes, the dysesthesia may be described as a pinprick or biting sensation.Asking the patient about pertinent controllable factors, such as the following, is important. Frequency of bathing, showering, and cleansing, and which soaps and cleansers are in contact with the skin. If the eruption persists despite therapy, behavioral changes, and treatment compliance, allergic contact dermatitis and irritant contact dermatitis and internal malignancy may require investigation.

**Physical.** Primary lesions: slightly scaly, inflamed, curvilinearly cracked and/or fissured skin most commonly involves the pretibial areas, but it may also occur on the thighs, on the hands, and on the trunk.Secondary lesions: excoriated, erythematous, edematous patches may result from rubbing or scratching.Bleeding fissures secondary to the disruption of dermal capillaries have been described in exaggerated eczema craquelé, which begins as superficial cracks in the epidermis. Generalized lesions: generalized or extensive asteatotic dermatitis presents with primary lesions and secondary excoriations.

**Lab Studies.** Appropriate laboratory studies are indicated for identified or suspected associated diseases.

**Histologic Findings.** Spongiosis and a varying amount of inflammatory dermal infiltrate similar to that of mild, subacute eczema are seen.

**Medical Care.** Patients should follow the methods listed below to improve the condition. Take short baths with decreased water temperature. Eliminate or reduce the use of soap on the involved areas. Avoid harsh skin cleansers. Apply petrolatum-based emollients following bathing, and use moisturizing agents liberally.Apply topical steroid ointments with or without polyethylene occlusion. Use humidifiers.

Topical steroid ointments with 24- to 48-hour occlusion with polyethylene or Unnaboot are the treatment of choice for the rapid resolution of asteatotic dermatitis. Many patients heal with mild topical steroids (class III-VI) alone, depending on the severity of the dermatitis, the patient's compliance with treatment, and the reduction in the use of soap and hot water to the involved areas. The liberal use of moisturizers, especially petrolatum-based preparations, alone or in combination with topical steroids for mild cases of asteatotic dermatitis is recommended.

**Prognosis.** Asteatotic dermatitis responds well to therapy; however, if the causative factors are not eliminated, recurrences are common.

## 6.6.Stasis Dermatitis

**Synonyms and related keywords:** venous eczema, chronic venous insufficiency

**Background.**Stasis dermatitis is a common inflammatory skin disease that occurs on the lower extremities in patients with chronic venous insufficiency. The condition typically affects middle-aged and elderly patients. It rarely occurs before the fifth decade of life, except in patients with acquired venous insufficiency due to surgery, trauma, or thrombosis. Stasis dermatitis is usually the earliest cutaneous sequela of venous insufficiency, and it may be a precursor to more problematic conditions, such as venous leg ulceration and lipodermatosclerosis.

**Causes (pathophysiology).**Stasis dermatitis occurs as a direct consequence of venous insufficiency. Disturbed function of the 1-way valvular system in the deep venous plexus of the legs results in backflow of blood from the deep venous system to the superficial venous system, with accompanying venous hypertension. This loss of valvular function can result from an age-related decrease in valve competency. Alternatively, specific events, such as deep venous thrombosis, surgery (e.g. vein stripping, harvesting of saphenous veins for coronary bypass), or traumatic injury, can severely damage the function of the lower-extremity venous system. The mechanism by which venous hypertension causes the cutaneous inflammation of stasis dermatitis has been extensively studied for decades. Several theories have been proposed.

The earliest theories regarding the cause of cutaneous inflammation in venous insufficiency centered on oxygen perfusion of lower-extremity tissues. Originally, an incompetent venous system was thought to lead to pooling of blood in the superficial veins, with reduced flow and therefore reduced oxygen tension in the dermal capillaries. This pooling hypothesis led to the term stasis dermatitis. It was believed that the decreased oxygen content of pooled blood led to hypoxic damage to the overlying skin.

The hypoxia/stasis theory was refuted by evidence that instead of pooled, stagnant blood with low oxygen tension, leg veins in patients with venous insufficiency have increased flow rates and high oxygen tension. Arteriovenous shunting could have accounted for these findings, but no evidence of shunting in patients with venous insufficiency was found. The complete lack of evidence to support a hypoxia/stasis theory has led many investigators to advocate the abandonment of the term stasis dermatitis.

Subsequent research focused on the role of lower-extremity microcirculation in the pathogenesis of skin damage due to venous insufficiency. In the 1970s and 1980s, increased venous hydrostatic pressure was found to be transmitted to the dermal microcirculation; this leads to increased permeability of dermal capillaries.

This increased permeability enables macromolecules, such as fibrinogen, to leak out into the pericapillary tissue; then, polymerization of fibrinogen to fibrin results in the formation of a fibrin cuff around dermal capillaries. It has been hypothesized

that this fibrin cuff serves as a barrier to oxygen diffusion, with resulting tissue hypoxia and cell damage. Subsequently, the phenomenon of fibrin cuff formation was found in more severe disease, such as venous ulceration. Fibrin cuffs are not found in ulcers due to causes other than venous hypertension. Decreased cutaneous fibrinolytic activity has been proposed to contribute to the formation of fibrin cuffs. The role of the fibrin cuff in causing skin changes of venous insufficiency has been questioned during the past decade. Specifically, the fibrin cuff has not been found to significantly decrease oxygen diffusion.

An alternate theory has emerged, implicating leukocyte trapping as a pathogenesis of stasis dermatitis. Venous hypertension has been shown to result in leukocyte sequestration in the microcirculation, with increased contact of leukocytes with the capillary endothelium. This leukocyte trapping may very well result in the release of inflammatory mediators, which further derange microvascular permeability and function. In addition, sludging of leukocytes may block dermal capillaries, leading to tissue ischemia. This is an attractive hypothesis; unlike previous theories, the leukocyte trapping hypothesis provides a direct link between dysfunctional venous circulation and cutaneous inflammation.

**Frequency.** Although not nearly as prevalent as skin cancer, dermatophytosis, or xerosis, stasis dermatitis affects a significant proportion of the elderly population.

**Age.** The risk of developing stasis dermatitis steadily increases with each passing decade; when considering only adults older than 70 years, the prevalence of stasis dermatitis may be greater than 20%.

**History.** Patients with stasis dermatitis typically present with an insidious onset of pruritus affecting 1 or both lower extremities.The medial ankle is most frequently involved, with symptoms progressing to involve the foot and/or the calf.The patient may offer a prior history of dependent leg edema. Factors that worsen peripheral edema (eg, congestive heart failure, long-standing hypertension with diastolic dysfunction) are often found in patients with stasis dermatitis.

**Physical:** Physical examination reveals erythematous, scaling, eczematous patches affecting the lower extremity. The medial ankle is most frequently and severely involved because of the fact that the medial ankle represents a watershed area with relatively poor blood flow compared with the rest of the leg. In advanced cases of stasis dermatitis, the inflammation may encircle the ankle and extend to just below the knee; this is sometimes referred to as stocking erythroderma. The dorsal part of the foot may be involved in severe cases.Involved skin in stasis dermatitis may exhibit the same changes as seen in other eczematous conditions.Severe, acute inflammation may result in exudative, weeping patches and plaques.Secondary infection can cause typical honey-colored crusting due to bacteria or monomorphous pustules due to cutaneous candidiasis.In long-standing lesions, lichenification and hyperpigmentation may occur as a consequence of chronic scratching and rubbing. In addition to lichenification and hyperpigmentation, chronic stasis dermatitis can show changes, such as skin induration, which may progress to lipodermatosclerosis with the classic inverted champagne bottle appearance.Another unique feature sometimes seen in chronic stasis dermatitis is

the development of violaceous plaques and nodules on the legs and dorsal part of the feet. These lesions frequently undergo painful ulceration and can be clinically indistinguishable from classic Kaposi sarcoma. This clinical appearance has led this entity to be called pseudo–Kaposi sarcoma or acroangiodermatitis.Stasis dermatitis frequently occurs along with a background of skin changes that are typical for patients with venous insufficiency.These skin changes include edema, varicosities, hyperpigmentation, atrophic patches (atrophie blanche), and diffuse red-brown discoloration representing deep dermal deposits of hemosiderin (from degraded, extravasated erythrocytes).These chronic changes persist regardless of the activity of stasis dermatitis.

**Complications.** Complications of chronic stasis dermatitis include cellulitis and non-healing venous ulcers.Direct consequences of stasis dermatitis include an increased incidence of allergic contact dermatitis, lower-extremity ulceration, lipodermatosclerosis, and id reaction (autoeczematization).

**Lab Studies.** Blood tests are generally not helpful in the management of stasis dermatitis, except in a patient where cellulitis and/or sepsis are suspected. An exception is the patient with stasis dermatitis due to venous thrombosis; patients with venous thrombosis need a thorough hematologic workup to rule out underlying hypercoagulability states.

**Imaging Studies.** Radiologic/Doppler studies. In patients with acute new-onset stasis dermatitis or in a young patient, investigating the dynamics of the deep venous circulation is prudent.Venous Doppler studies may reveal deep venous thrombosis or severe valve damage due to past thrombosis. Of course, the consequences of an unrecognized acute or subacute deep venous thrombosis may be catastrophic.

**Histologic Findings.** Skin biopsy of stasis dermatitis, although rarely indicated, shows an acute or subacute dermatitis. Acute lesions may exhibit a superficial perivascular lymphocytic infiltrate, epidermal spongiosis, serous exudate, scale, and crust. Chronic lesions may show epidermal acanthosis with hyperkeratosis. The dermis is characterized by deep dermal aggregates of siderophages due to uptake of hemosiderin from degraded erythrocytes. Dermal capillaries are frequently dilated; long-standing lesions show intimal thickening of small arterioles and venules along with dermal fibrosis.

A special consideration in chronic stasis dermatitis where biopsy may be necessary is the development of acroangiodermatitis (pseudo–Kaposi sarcoma). The violaceous plaques and nodules of acroangiodermatitis may be clinically indistinguishable from classic Kaposi sarcoma, especially when occurring in an elderly man. Biopsy samples show changes typical of stasis dermatitis, along with a proliferation of capillaries and fibroblasts. However, the vascular slits and the atypical endothelial cells that are seen in classic Kaposi sarcoma are absent.

**Medical Care.** ***Compression therapy.*** Although extensive work has been completed in the study of treatment of venous ulcers, no large, well-controlled trials examine the treatment of stasis dermatitis. The overall mainstay of treatment has always been aimed at lessening the clinical impact of the underlying venous

insufficiency, which is typically accomplished with compression therapy. Assessing the patient's peripheral arterial circulation (clinically or with a Doppler study) before recommending compression therapy is important; adding compression to a leg with compromised arterial circulation could increase claudication and put the patient at risk for ischemic damage. Compression is generally accomplished by means of specialized stockings that deliver a controlled gradient of pressure (measured in mm Hg) to the affected leg. More aggressive compression can be performed by using elastic wraps; compression (Unna) boots; and more sophisticated devices, such as end-diastolic compression boots. Frequent leg elevation is a necessary adjunct to leg compression. Counseling patients that compression therapy must be maintained on a lifelong basis is important.

***Topical therapy.*** Topical treatment of stasis dermatitis has much in common with the treatment of other forms of acute eczematous dermatitis. Weeping lesions can be treated with wet-to-damp gauze dressings soaked with water or with a drying agent, such as aluminum acetate. Topical corticosteroids are frequently used for reducing inflammation and itching in acute flares; mid-potency corticosteroids, such as triamcinolone 0.1% ointment, are generally effective. Be wary of the use of high-potency topical corticosteroids in stasis dermatitis because the chronically inflamed skin can increase the risk of systemic absorption and because steroid-induced cutaneous atrophy can predispose the patient to ulceration. Systemic corticosteroids are not part of stasis dermatitis treatment, although they may be required in very severe cases of widespread autoeczematization.

***Prevention/management of infection.*** Be wary of infection in stasis dermatitis; this becomes more problematic when using topical corticosteroids, which make the patient more susceptible to infection. Open excoriations and erosions should be treated with a topical antibiotic, such as bacitracin or polysporin. Obvious superficial impetiginization should be treated with topical mupirocin or a systemic antibiotic with activity against *Staphylococcus* and *Streptococcus* species (e.g. dicloxacillin, cephalexin, cefadroxil, levofloxacin). Expanded coverage may be necessary in patients who are immunocompromised. Suspected deep cellulitis should always be treated with oral or intravenous antibiotics. Necrotizing fasciitis would be a rare complication but is a surgical emergency.

***Complications of treatment.*** The development of contact dermatitis is especially problematic in the treatment of patients with stasis dermatitis. All of the above-mentioned topical treatments, including bacitracin and topical corticosteroids, have been reported to cause contact sensitization in patients with stasis dermatitis. Consider contact dermatitis in any patient with stasis dermatitis who becomes clinically worse despite appropriate topical treatment.

***Long-term management.*** Patients with chronic, quiescent stasis dermatitis can be treated with bland topical emollients to maximize epidermal moisture. Plain white petrolatum is an inexpensive occlusive moisturizer that is very effective and, importantly, does not contain any contact sensitizers.

Recent new theories regarding the pathogenesis of cutaneous inflammation in venous insufficiency have led to the investigation of systemic therapies, which

have been hypothesized to have beneficial modulating effects on neutrophil function. Treatments, such as prostaglandin E1 (PGE1) and pentoxifylline, have been studied in the treatment of venous ulcers; it is hypothesized that these medications decrease cytokine-mediated neutrophil activation, leading to reduced inflammation. However, even if these systemic therapies are proven unequivocally effective, it is unlikely that their use will extend beyond the scope of treatment of recalcitrant venous ulcers.

**Consultations.**Uncomplicated stasis dermatitis is usually managed in the dermatologist's office. A consultation with a vascular surgeon may be required, especially when an underlying surgically correctable vascular abnormality is suspected.A consultation with a hematologist may be needed when treating a patient with stasis dermatitis due to deep venous thrombosis; cases such as these may be secondary to congenital or acquired hypercoagulable states.

**Patient Education.**Patients should be educated regarding the underlying cause of their condition and the permanent nature of venous valvular insufficiency.

# VII. Erythema Multiforme and Stevens-Johnson syndrome

**Synonyms and related keywords:** EM, Stevens-Johnson syndrome, SJS, erythema multiforme major, EM major, erythema multiforme minor, EM minor, herpes-induced EM major, herpes-associated erythema multiforme, herpes-associated EM, drug-induced SJS, drug-induced Stevens-Johnson syndrome

**Background:** Erythema multiforme (EM) is an acute self-limited eruption characterized by a distinctive clinical eruption, the hallmark of which is the iris or target lesion. EM may present within a wide spectrum of severity. EM minor represents a localized eruption of the skin with mild or no mucosal involvement, corresponding to the initial description of von Hebra. EM major and Stevens-Johnson syndrome (SJS) are more severe mucosal and skin diseases and are potentially life-threatening disorders.

Recently, international collaborators have suggested that EM and SJS could be separated as 2 distinct clinical disorders with similar mucosal reactions but different patterns of cutaneous lesions. The clinical pictures are as follows:

– Mucosal erosions plus typical or raised atypical targets and epidermal detachment involving less than 10% of the body surface. The lesions are usually located on the extremities and/or the face. This characterizes herpes-induced EM major.

– Mucosal erosions plus widespread distribution of flat atypical targets or purpuric macules and epidermal detachment involving less than 10% of the body surface. The lesions may be present on the trunk, the face, and the extremities. These are characteristic findings of drug-induced SJS.

**Pathophysiology:** The pathophysiology of EM is still not completely understood; however, herpes-associated EM (HAEM) appears to represent the result of a cell-mediated immune reaction associated with herpes simplex virus (HSV) antigen. The immunologic reaction affects HSV-expressing keratinocytes. Cytotoxic effector cells, $CD8^+$ T lymphocytes in the epidermis, induce apoptosis of scattered keratinocytes and lead to satellite cell necrosis. Neighboring epidermal cells are human leukocyte antigen DR (HLA-DR) positive. A relationship exists between human leukocyte antigen (HLA) types A33, B35, B62 (B15), DR4, DQB1*0301, DQ3, and DR53 and recurrent EM. HLA-DQ3 has been proven to be especially related to recurrent EM, and it may be a helpful marker for distinguishing HAEM from other diseases with EM-like lesions.

**Frequency:** The exact incidence of EM is unknown; as many as 1% of dermatologic outpatient visits are for EM.

**Mortality/Morbidity:** Most cases of EM minor subside completely within 2-3 weeks without any complications. The mortality rate of EM major is reportedly less than 5%, and clearing requires a longer time than EM minor. EM major usually takes 3-6 weeks to heal.

**Age:** The highest incidence is in the second to fourth decades of life, with 20% of cases occurring in children and adolescents.

**Causes.**Many suspected etiologic factors have been reported to cause EM (and many were published at a time when a distinction between EM major and SJS was not made). They are listed below. EM and SJS are both caused by drugs, but infectious agents are considered to be the major cause of EM. Today, EM minor is regarded as being triggered by HSV in nearly 100% of cases; many instances of idiopathic EM minor may be precipitated by subclinical HSV infection. A herpetic etiology also accounts for 55% of cases of EM major. Among the other infections, *Mycoplasma* infection appears to be a common cause. Drugs are reported in many documented cases of SJS and EM major. Sulfa drugs are the most common triggers. A slow acetylator genotype is a risk factor for sulfonamide-induced SJS. Prophylactic anticonvulsants after surgery for a brain tumor combined with cranial irradiation may result in life-threatening SJS.

***Infections. Bacterial*** - Bacille Calmette-Guérin (BCG) vaccination, borreliosis, catscratch disease, diphtheria, hemolytic streptococci, legionellosis, leprosy, *Neisseria meningitidis, Mycobacterium avium* complex, pneumococcus, *Proteus* species, *Pseudomonas* species, *Salmonella* species, *Staphylococcus* species, syphilis, tuberculosis, tularemia, *Vibrio parahaemolyticus,* Vincent disease, *Yersinia* species, rickettsial infections, *Mycoplasma pneumonia.****Chlamydial*** - Lymphogranuloma venereum, psittacosis.***Fungal*** - Coccidioidomycosis, dermatophytosis, histoplasmosis.***Parasitic*** - *Trichomonas* species, *Toxoplasma gondii.****Viral*** - Adenovirus, coxsackievirusB5, cytomegalovirus, echoviruses, enterovirus, Epstein-Barrvirus, hepatitisA, hepatitisB, hepatitisC, herpessimplex, influenza, measles, mumps, paravaccinia, parvovirusB19, poliomyelitis, vaccinia, varicella-zoster, variola.

***Drugs.*** Antibiotics - penicillin, ampicillin, tetracyclines, amoxicillin, cefotaxime, cefaclor, cephalexin, ciprofloxacin, erythromycin, minocycline, sulfonamides, trimethoprim-sulfamethoxazole, vancomycin**.** Anticonvulsants - barbiturates, carbamazepine, hydantoin, phenytoin, valproic acid.Antipyretics - analgesics, especially aspirin.Antituberculoids - rifampicin, isoniazid, thiacetazone, pyrazinamide.Others - acarbose, albendazole, allopurinol, arsenic, bromofluorene, chinine, cimetidine, clofibrate, corticosteroids, diclofenac, didanosine, dideoxycytidine, diphosphonate, estrogen, etretinate, fluconazole, griseofulvin, gabapentin, granulocyte-macrophagecolony-stimulatingfactor, hydralazine, indapamide, indinavir, lamotrigine, methazolamide, mefloquine, methotrexate, meprobamate, mercurials, minoxidil, nifedipine, nevirapine, nitrogenmustard, nystatin, nonsteroidalanti-inflammatorydrugs (NSAIDs), phenolphthalein, piroxicam, pyritinol, progesterone, potassiumiodide, sulindac, suramin, saquinavir, thiabendazole, thiouracil, terbinafine, theophylline, verapamil.

***Contactants*** - ammoniated mercury, budesonide, bufexamac, capsicum, chloromethylnaphthalene, desoximethasone, dinitrochlorobenzene (DNCB), disperse blue 124, diphenylcyclopropenone, fire sponge (*Tedania ignis*), isopropyl-*p*-phenylenediamine of rubber, nitrogen mustard, oxybenzone, phenylbutazone,

poison ivy, proflavin, resin, rosewood, sesquiterpene lactones in herbal medicine, triamcinolone acetonide. ***Immunologic disorders*** - transient selective C4 deficiency of infancy. ***Mechanical factors***– tattooing. ***Foods*** - salmon berries. ***Physical factors*** - radiotherapy, cold, sunlight. ***Others*** - collagen diseases, vasculitides, non-Hodgkin lymphoma, leukemia, multiple myeloma, myeloid metaplasia, polycythemia.

**History.**The prodromal symptoms are mild or absent in EM minor and may present as a mild nonspecific upper respiratory infection. The abrupt onset of a rash usually occurs within 3 days, starting on the extremities symmetrically with centripetal spreading.

– In EM major, 50% of patients have nonspecific prodromes, including moderate fever, general discomfort, cough, sore throat, vomiting, chest pain, and diarrhea. These symptoms are usually present for 1-14 days preceding the eruption. The lesions begin on the acral areas and spread similarly to the distribution of EM minor.

– Prominent mucosal involvement may occur in EM major. Erosions of the oral mucosa may result in difficulty in eating, in drinking, and in opening the mouth. Eye involvement may cause lacrimation and photophobia. Genital lesions are painful and may result in urinary retention.

– Skin tenderness is absent with an occasional mild burning sensation and itching.

– A localized form of EM has been reported at the site of marrow aspiration.

– One half of children who are affected have a history of herpes labialis or herpes genitalis. While the onset usually precedes EM by 3-14 days, it may still be present at the onset of EM. HAEM can be precipitated by exposure to the sun.

**Physical:** The hallmark of EM is a target lesion with variable mucous membrane involvement.

***Skin lesion.*** The initial lesion is a dull red macule or urticarial plaque expanding slightly to a maximum of 2 cm over 24-48 hours. In the center, a small papule, vesicle, or bulla develops, flattens, and then may clear. The intermediate ring develops and becomes raised, pale, and edematous. The periphery gradually changes to become cyanotic or violaceous and forms a typical concentric target lesion.Some lesions are atypical targets that consist of only 2 concentric rings.Polycyclic or arcuate lesions may occur.The Koebner phenomenon may be observed.The Nikolsky sign is negative.

***Skin distribution.*** The lesions appear predominantly on the extensor surfaces of the acral extremities and spread centripetally. The palms, the neck, and the face are frequently involved. Lesions of the soles and flexural aspects of the extremities are less frequent. A zosteriform distribution has been observed.

***Mucosal lesions.*** Mucosal involvement is present in as many as 70% of patients with EM. The degree is usually mild with limitation to one mucosal surface.Oral lesions are the most common, with the lips, the palate, and the gingiva often affected. More severe erosions of at least 2 mucosal surfaces are seen in EM major and are characterized by a hemorrhagic crusting of the lips and ulceration of the

non-keratinized mucosa. Extensive painful mucosal involvement with few or no skin lesions may be seen.Eye involvement is usually mild and may present as red conjunctivae, chemosis, and lacrimation.The genital areas may have painful, hemorrhagic bullae and erosions.Mucosal lesions usually heal without sequelae. The mucosal involvement in SJS is more severe and extensive than in EM major.Generalized lymphadenopathy often accompanies EM major.

**Complications.**Most patients have an uncomplicated course, with the exception of hosts who are immunocompromised and those with secondary bacterial infections of the skin or the mucosa.Severe oral involvement may be accompanied by difficulty in consuming food and fluid and can result in dehydration. Ocular complications may manifest as purulent conjunctivitis, dry eyes, anterior uveitis, panophthalmitis, scarring of the conjunctivae, symblepharon, and blindness.Vaginal and urethral lesions are infrequent. The erosions may cause urinary retention and phimosis. Hematocolpos is the result of genital lesions in teenage females. Severe scarring of the genitourinary tract may cause vaginal and urethral stenosis.

**Lab Studies.**Complete blood count; electrolyte levels; BUN determination; erythrocyte sedimentation rate (ESR); liver function tests; and cultures from blood, sputum, and erosive areas are indicated in severe cases of EM major. In severe cases, elevated ESR, moderate leukocytosis, and mildly elevated liver transaminase levels may be found.Specific HSV antigens have been detected within keratinocytes by immunofluorescence study. The HSV DNA has been identified primarily within the keratinocytes by polymerase chain reaction amplification.

**Procedures.**A histopathologic examination of a cutaneous punch biopsy should be performed to confirm the diagnosis and to rule out the other differential diagnoses.

**Histologic Findings:** The early lesion of EM is characterized by infiltration of lymphocytes at the dermal-epidermal interface with accompanying exocytosis and spongiosis in the epidermis. Individual eosinophilic necrotic keratinocytes may be scattered and surrounded by lymphocytes (satellite cell necrosis). The dermal changes include edematous papillary dermis, ectatic and swollen endothelial cells of the vessels, and extravasation of the red blood cells.

As lesions progress, partial-to-full-thickness epidermal necrosis, intraepidermal vesiculation, subepidermal blisters due to spongiosis, ballooning, vacuolar degeneration of the junctional zone, and severe papillary edema occur. Lymphohistiocytes ($CD4^+$ more than $CD8^+$ T lymphocytes) with a few neutrophils and occasional eosinophils comprise the dermal inflammatory infiltrate. Recently, an observation revealed that acrosyringeal keratinocyte necrosis and dermal inflammation containing eosinophils may occur in drug-related cases.

**Medical Care:** Identification of the cause should be made if possible. If a drug is suspected, it must be withdrawn. Infections should be appropriately treated after cultures and/or serologic tests have been performed. For all forms of EM, symptomatic treatment, including oral antihistamines, analgesics, local skin care, and soothing mouthwashes, is of great importance. Topical steroids may be

considered.A liquid diet and intravenous fluid therapy may be necessary. Oral antacids may be helpful for discrete oral ulcers.Electrolytes and nutritional support should be started as soon as possible. The use of liquid antiseptics, such as 0.05% chlorhexidine, during bathing is preferable. Topical treatment, including that for genital involvement, may be performed with a gauze dressing or a hydrocolloid. Local supportive care for eye involvement is important and includes topical lubricants for dry eyes, sweeping of conjunctival fornices, and removal of fresh adhesions.

Systemic corticosteroids are controversial, and some believe they may predispose to complications. Beneficial effects of hemodialysis, plasmapheresis, cyclosporin, immunoglobulin, levamisole, thalidomide, dapsone, and cyclophosphamide have been documented in case reports.The most severe cases should be managed in intensive care or burn units.

**Consultations.**Obtain a dermatologic consultation for diagnosis and management. Consult an internal medicine specialist or a pediatric specialist for evaluation of the underlying causes of disorders and systemic sequelae.Obtain an early ophthalmologic consultation for evaluation and management of ocular involvement.EM major may require hospitalization for the treatment of complications and sequelae.

**Prevention.**Sulfonamide-containing ointments should be avoided.Prophylaxis for recurrence of HAEM should be considered in patients with more than 5 attacks per year.Low-dose acyclovir (200 mg qd to 400 mg bid) can be effective for recurrence of HAEM, even in subclinical HSV infection. In children, the dosage of 10 mg/kg/d may be considered.Prophylaxis may be required for 6-12 months or longer. If unresponsive, continuous therapy of valacyclovir (500 mg bid) has been reported to be effective.

**Prognosis.** In EM minor, the lesions ultimately subside within 2-3 weeks without scarring. The recurrence of EM minor is common and varies between 1 and 10 times per year.EM major has a mortality rate of less than 5%. It usually takes a more protracted course than EM minor; clearing may require 3-6 weeks. Skin lesions usually heal with hyperpigmentation and/or hypopigmentation. Scarring is usually absent, except after secondary infection.Healing of the mucosal areas is usually complete. Scars and strictures of the esophageal, urethral, vaginal, and anal mucosa rarely occur.Severe eye complications may result in permanent blindness.

## 8. Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis

**Synonyms and related keywords:** erythema multiforme, EM, SJS, TEN

**Background:** Toxic epidermal necrolysis (TEN) is an acute dermatologic disease, the presentation of which may constitute a true emergency. The disorder is characterized by widespread erythematous macules and targetoid lesions; full-thickness epidermal necrosis, at least focally; and involvement of more than 30% of the cutaneous surface. Commonly, the mucous membranes are also involved.

Nearly all cases of TEN are induced by medications, and the mortality rate can approach 40%.

Stevens-Johnson syndrome (SJS) may also present as a dermatologic emergency characterized by purpuric macules and targetoid lesions; full-thickness epidermal necrosis, although with lesser detachment of the cutaneous surface; and mucous membrane involvement. As with TEN, medications are important inciting agents, although *Mycoplasma* infections may induce some cases. The mortality rate is much lower and approaches 5% of cases.

Erythema multiforme (EM) is generally a far more benign process characterized by target or targetoid lesions, with or without blisters, in a symmetric acral distribution. Oral lesions are common. Severe presentations may have widespread involvement of the mucous membranes and epidermal detachment with a loss of less than 10% of the cutaneous surface. Most cases are secondary to prior infection with a herpes virus. The condition generally has low morbidity and no mortality and is often recurrent. SJS may have features of both EM and TEN, which has led to confusion in nosology.

SJS and TEN may represent a spectrum of a single disease process. Some evidence suggests that EM may be an entirely distinct disorder. This article discusses SJS and TEN.

**Pathophysiology:** SJS and TEN are often drug induced, but the pathophysiologic mechanism is unknown. A number of theories have been proposed that may have implications for treatment. Patients and their first degree-relatives may have genetic defects in their metabolic pathways that lead to the accumulation of toxic metabolites. For example, patients with sulfonamide-induced TEN have been shown to have a slow acetylator genotype, resulting in increased production of sulfonamide hydroxylamine via the P-450 pathway. These drug metabolites may have direct toxic effects or act via a hapten-mediated mechanism to break self-tolerance to endogenous proteins.

Apoptosis of keratinocytes has been proposed secondary to a cell-mediated cytotoxic reaction. Keratinocyte apoptosis is rare in the healthy epidermis, but it has been shown to be increased in TEN. In 1997, Inachi et al demonstrated perforin-mediated apoptosis in patients with SJS. Perforin, a pore-making monomeric granule released from natural killer cells and cytotoxic T lymphocytes, kills target cells by forming polymers and tubular structures not unlike the membrane attack complex of the complement system.

A second proposed mechanism of apoptosis involves interaction between a cell-surface death receptor, such as Fas, and its receptive ligand, to form a Fas ligand (FasL). In 1998, Viard et al demonstrated high concentrations of soluble Fas ligand (sFasL) in TEN sera. In vitro, target cell death was blocked by a FasL-blocking antibody and by antibodies present in pooled human intravenous immunoglobulin (IVIG). An open trial of IVIG in 10 patients with TEN resulted in a halt of progression within 24-48 hours, with no mortality.

**Mortality/Morbidity:** SJS may prove fatal in roughly 5% of patients; TEN may prove fatal in as many as 40% of patients. Sepsis and respiratory distress are the

most common complications and ultimately the direct causes of death. Important prognostic factors include the percentage loss of body surface area (BSA), age, persistent neutropenia (defined as neutropenia lasting >5 d), hypoalbuminemia (usually <2 g/dL), and persistent azotemia. Among 247 French patients, only 1 out of 70 died when BSA involvement was less than 10%. In contrast, the mortality rate was 11% for patients with 10-30% BSA involvement and 35% for patients with BSA involvement exceeding 30%.

While some patients rapidly progress to lose very large areas of the epidermis in a matter of days, the process suddenly ceases in others and re-epithelialization begins a few days later. Predicting the course of disease in a given patient at the initial presentation is not possible. Re-epithelialization is usually complete within 3 weeks, but pressure and mucosal areas may remain eroded and crusted for 2 weeks or longer.

Survivors of SJS/TEN may experience numerous long-term sequelae; the most disabling are those of the eye. Cicatrization of conjunctival erosions may lead to inverted eyelashes, photophobia, a burning sensation in the eyes, watery eyes, a sicca-like syndrome, and corneal and conjunctival neovascularization. As many as 40% of survivors of TEN have residual potentially disabling lesions that may cause blindness.

Cutaneous lesions may resolve with a patchwork of hyperpigmentation and hypopigmentation. Fingernails and toenails may regrow abnormally. Lesions of the genitourinary system may lead to phimosis or vaginal synechiae.

**Age:** TEN occurs in all age groups, including newborns. Because drug exposure increases with age, SJS and TEN occur more frequently in the older population. Also, adults might be metabolically more susceptible to such drug reactions than children. However, only 54% of cases of SJS could be attributed to drugs, and some cases of EM, which typically affects younger patients, were likely included in the analysis. Lastly, HIV infection is associated with TEN.

**Causes:** Most cases of SJS/TEN are drug induced. In establishing a drug exposure timeline, agents administered within 1-3 weeks are most suspect, although longer or shorter times do not necessarily rule out a particular medication. A case-control study of 245 patients and 1,147 control subjects in Europe identified potential drug triggers.

For medications used on a short-term basis, the relative risk was greatest for trimethoprim-sulfamethoxazole and other sulfonamide antibiotics, chlormezanone, aminopenicillins, quinolones, and cephalosporins.

Among drugs used long term, the greatest risk of SJS/TEN was seen in the first 2 months of use. The agents posing an increased risk were carbamazepine, phenobarbital, phenytoin, valproic acid, oxicam non-steroidal anti-inflammatory drugs, allopurinol, and corticosteroids. The greatest excess risk was 4.5 cases per million users in 1 week for sulfonamides.

Epidemiologic studies in France have shown a greater risk of TEN in patients infected with HIV, especially those with acquired immune deficiency syndrome

(AIDS). In the greater Paris area, 15 cases of AIDS-associated TEN occurred over a 6-year period, whereas 0.04 cases would be expected in the general population. This finding may be due to the increased use of sulfonamides in patients infected with HIV and abnormal patterns of production or detoxification of drug metabolites.

TEN has been reported in patients with systemic lupus erythematosus, but these limited cases may be a mere coincidence. Infections with herpesvirus, *Mycoplasma pneumoniae,* or *Yersinia* have also been reported in patients with SJS, but these patients may have had EM. Other reported associations include leukemia, lymphoma, ulcerative colitis, and Crohn disease.

**History.**Constitutional symptoms, such as fever, cough, or sore throat, may appear 1-3 days prior to any cutaneous lesions.Patients may complain of a burning sensation in their eyes, photophobia, and a burning rash that begins symmetrically on the face and the upper part of the torso.Delineation of a drug exposure timeline is essential, especially in the 1-3 weeks preceding the cutaneous eruption.

**Physical.*Primary lesions.***The initial skin lesions of SJS/TEN are poorly defined erythematous macules with darker purpuric centers. The lesions differ from classic target lesions of EM by having only 2 zones of color: central dusky purpura or a central bulla, with surrounding macular erythema. A classic target lesion has 3 zones of color: central dusky purpura or a central bulla, a surrounding edematous pale zone, and a surrounding macular erythema.Lesions, with the exception of central bullae, are typically flat. Lesions of EM are more likely to be palpable.Less frequently, the initial eruption may be scarlatiniform. Flaccid blisters are typically present with full-thickness epidermal necrosis.Non-denuded areas have a wrinkled paper appearance. Nikolsky sign is easily demonstrated by applying lateral pressure to bullae.***Arrangement***: individual macules are found surrounding large areas of confluence.***Distribution***: lesions begin symmetrically on the face and the upper part of the torso and extend rapidly, with maximal extension in 2-3 days. In some cases, maximal extension can occur rapidly over hours. Lesions may predominate in sun-exposed areas. Full detachment is more likely to occur in areas subjected to pressure, such as the shoulders, the sacrum, or the buttocks.Painful edematous erythema may appear on the palms and the soles. The hairy scalp typically remains intact, but the entire epidermis, including the nail beds, may be affected.

A recent classification proposes that epidermal detachment in SJS is limited to less than 10% of the BSA. Overlapping SJS/TEN has more extensive confluence of erythematous and purpuric macules, leading to epidermal detachment of 10-30% of the BSA. Classic TEN has epidermal detachment of more than 30%.An uncommon form of TEN (TEN without spots) lacks targetoid lesions, and blisters form on confluent erythema. Greater than 10% epidermal detachment is required for diagnosis of these cases.In contrast, bullous EM, which has been previously grouped with SJS, may have epidermal detachment of less than 10% of the BSA, but typical target lesions or raised atypical targets are localized primarily in an acral distribution.

***Secondary lesions***: areas of denuded epidermis are dark red with an oozing surface.

***Mucous membranes***: mucous membrane involvement is present in nearly all patients and may precede skin lesions, appearing during the prodrome.Painful oral erosions cause severe crusting of the lips, increased salivation, and impaired alimentation. Involvement of the genitalia may lead to painful micturition. Lesions have been reported in the oropharynx, the tracheobronchial tree, the esophagus, the GI tract, the genitalia, and the anus. Intact expectorated cylindrical casts of bronchial epithelium have been reported. Patients may develop a profuse protein-rich diarrhea. Internal involvement is not necessarily limited to patients with extensive cutaneous involvement.

***Ocular lesions***: ocular lesions are especially problematic because they have a high risk of sequelae. Initially, the conjunctivae are erythematous and painful. The lids are often stuck together, with efforts to loosen them resulting in tearing of the epidermis. Pseudomembranous conjunctival erosions may form synechiae between the eyelids and the conjunctivae. Keratitis, corneal erosions, and a sicca-like syndrome may develop.

**Complications.**Ocular complications must be taken seriously. Failure to lyse adhesions and treat keratitis and corneal erosions can result in blindness. Even meticulous ophthalmologic care can still eventuate long-term sequelae. Cicatrization of conjunctival erosions may lead to inverted eyelashes, photophobia, a burning sensation in the eyes, watery eyes, a sicca-like syndrome, and corneal and conjunctival neovascularization. As many as 40% of survivors of TEN have residual potentially disabling lesions that may cause blindness.

TEN and SJS may result in cutaneous scarring, especially in the setting of impetiginization and inadequate wound care. Such scarring may eventuate in cosmetically problematic healing and, if severe, may lead to contractures and functional impairment. Lesions of the genitourinary system may lead to phimosis or vaginal synechiae. Ideally, patients are cared for in a burn unit, where meticulous wound care can be provided.

**Lab Studies.**The initial laboratory workup includes a CBC count, a chemistry profile, liver enzyme studies, renal function studies, prothrombin time, activated partial thromboplastin time, and cultures of blood and areas of denuded skin.

**Imaging Studies.**A baseline chest radiograph should be obtained because tracheobronchial involvement and respiratory distress are frequent complications.

**Procedures.**Bronchoscopy may be considered to verify involvement of the respiratory tract, but further epithelial trauma may be induced.Similarly, an upper GI series, esophagogastroduodenoscopy, and colonoscopy may be needed to confirm involvement of the GI tract.

**Histologic Findings:** Diagnosing SJS/TEN and ruling out staphylococcal scalded skin syndrome or a blistering disorder are important because the prognosis and the course differ markedly. To this end, routine or fresh-frozen section specimens of sloughed epidermis should be obtained for histologic examination. Full-thickness

epidermal necrosis is consistent with TEN/SJS, whereas a subcorneal split is consistent with staphylococcal scalded skin syndrome.

A biopsy sample of fully developed lesions reveals full-thickness epidermal necrosis with involvement of the sweat ducts, relative sparing of the hair follicles, and little alteration of the dermis. Immunofluorescence study results are negative.

**Medical Care:** Patients with SJS/TEN should be treated in an ICU or burn unit under the coordinated care of an ICU team and consultants. Hospitalization should be considered for patients with an initially benign presentation of SJS because predicting which patients will progress to more severe manifestations or TEN is not possible. The broad principles of management are fluid replacement, nutritional supplementation, sterile technique, and wound care. Studies have shown that early care by or transport to a burn center significantly reduces the mortality rate.

The first step in medical treatment is withdrawal of causative drugs. Retrospective studies have indicated that early withdrawal decreases the mortality rate. Implicated medications are listed above.

The use of corticosteroids in the management of the SJS/TEN spectrum is one of the most controversial areas in dermatology. Administration early in the course of disease has been advocated, but multiple retrospective studies demonstrate no benefit or higher rates of morbidity and mortality.

A number of studies support the use of IVIG in the treatment of TEN. The authors recommended early infusion of IVIG at a total dose of 3 g/kg over 3 consecutive days (1 g/kg/d for 3 d).

An open study from the trauma literature demonstrated the efficacy of cyclosporine. All patients in the cyclosporine group survived versus 50% surviving in the cyclophosphamide group. Given a mortality rate of approximately 30% in patients not infected with HIV with TEN, cyclosporine may prove to be a life-saving therapy, but randomized controlled trials are needed to make definitive recommendations.

***Fluid replacement***: fluid rehydration is essential because epidermal loss results in massive fluid shifts and dehydration.

***Nutritional supplementation***: aggressive nutritional support should be initiated because protein losses through denuded skin are massive, predisposing the patient to complications and retardation of re-epithelialization.

***Sterile technique***. Epidermal loss predisposes patients to infection and sepsis. Sterile technique is essential to prevent complications from endogenous and exogenous sources. Silver sulfadiazine must be avoided because sulfonamides are a frequent inciting drug in TEN. Broad-spectrum prophylactic antibiotics are not recommended.

***Wound care.*** Debridement of all necrotic epidermis with replacement by using biologic dressings, such as collagen-based substitutes or porcine xenografts, is recommended. Some physicians use biologic dressings only on denuded skin, leaving necrotic intact epidermis in place. Adhesive tapes should be avoided

because further skin loss may occur at the site of application. Oral care and application of antiseptics may be necessary.

***Consultation with an ophthalmologist*** is essential. Frequently applied eye drops may be necessary with daily blunt disruption of synechiae. Eye drops must not contain sulfonamides because they are frequently implicated in TEN.

***Other supportive treatment.*** Because epidermal slough leads to massive heat loss, the environmental temperature should be increased to 30-32°C. Heated antiseptic baths, heat shields, infrared lamps, and air-fluidized beds may decrease heat losses. As a caveat, air-fluidized beds can pose an evaporative effect, and fluid status should be corrected prior to use.

**Consultations.**Obtain an early consultation with a dermatologist because the prognosis and the course differ markedly for TEN/SJS and other diseases in the differential diagnosis.Consultation with an ophthalmologist is essential because early lesions may be subclinical.Consultation with a pulmonologist is prudent because interstitial edema may be evident on chest radiographs prior to the appearance of clinical symptoms.Consultation with a GI specialist is appropriate in cases of suspected involvement of the GI tract.

**Prognosis:** The prognosis is largely a function of the degree of skin sloughing. As the percentage of skin sloughing increases, the mortality rate dramatically worsens. In some patients for unknown reasons, the disease process simply stops progressing and rapid epithelialization ensues. For patients experiencing sloughing over a large area of their skin surface, the mortality rate is much higher.

If a causative drug can be identified, early discontinuation is essential. Early discontinuation is associated with improved survival, especially for short-acting medications. Patients exposed to causative drugs with long half.

# VII. ATOPIC DERMATITIS AND RELATED DISORDERS

## 7.1. Atopic Dermatitis

**Synonyms and related keywords:** AD, eczema, immunologic skin disorder.

**Background:** Atopic dermatitis (AD) is a chronically relapsing skin disorder with an immunologic basis. The clinical presentation varies from mild to very severe. In the worst cases, AD may interfere with normal growth and development. Treatment consists of adequate skin hydration, avoidance of allergenic precipitants, topical anti-inflammatory medications, systemic antihistamines, and antibiotic coverage of secondary infections. Although often used interchangeably, the terms eczema and AD are not equivalent. Eczema is a reaction pattern with various causes, the most common pediatric cause being AD. Other causes of eczematous dermatitis include allergic contact dermatitis, irritant contact dermatitis, seborrheic dermatitis, nummular eczema, dyshidrotic eczema, asteatotic eczema, and lichen simplex chronicus. Eczematous reactions can be classified as acute, subacute, or chronic, depending on historical and physical characteristics.

**Pathophysiology.**The etiology of AD remains unclear. Histologically, AD has been shown to be a complex inflammatory process involving mast cells, lymphocytes, and infiltrating leukocytes. One causative theory is that AD results from a hyperactive T helper cell 2 (Th2) and down-regulation of T helper cell 1 (Th1) activity. Th2 cells normally secrete interleukin (IL)–4, IL-5, and IL-13, of which IL-4 and IL-13 serve to promote the synthesis of immunoglobulin E (IgE) from B lymphocytes and to activate the vascular endothelium. IL-5 enhances eosinophil-mediated responses. This theory is supported by the frequent occurrences of elevated serum IgE levels and peripheral blood eosinophilia in AD patients. Furthermore, evidence is accumulating that administration of IL-2 or gamma-interferon, the cytokines of the Th1 immune response system, to atopic patients results in improvement in disease severity.

Another theory is that AD may be a result of problems with fatty acid metabolism. Specifically, deficient levels of omega-6 fatty acids have been observed in the blood and adipose tissues of individuals affected by AD as well as in the breast milk of mothers of some affected infants. Infants fed formula, which has a relatively low yield of omega-6 fatty acids in comparison with breast milk, have a higher incidence of AD than infants fed human milk. Furthermore, prostaglandin E1 (PGE1) and prostaglandin E2 (PGE2), major metabolites of omega-6 fatty acid biosynthesis, have been shown to suppress synthesis of IgE and are necessary for the optimal stimulation of Th1 cell activities by thymic hormones.

**Frequency:** AD occurs in approximately 10-15% of children. Areas in the Western Hemisphere have prevalence estimated at 10%, while areas in Asia have much lower disease prevalence. Interestingly, populations that migrate from areas of low prevalence to areas of higher prevalence have shown an increased incidence of AD, bolstering the idea of strong environmental influences in the development

of AD. Children with concurrent asthma or hay fever have a 30-50% incidence of developing AD.

**Age:** AD may occur in people of any age, but it often starts in infants aged 2-6 months. Seventy-five percent of individuals experience marked improvement in the severity of AD by age 10-14 years, but the remaining 25% continue to have relapses during their adult life.

**Cause.**The etiology of AD appears to be linked both to genetic causes and to environmental agents. The prevalence of AD in children with 1 affected parent is 60% and rises to nearly 80% for children of 2 affected parents. Additionally, nearly 40% of patients with newly diagnosed cases report a positive family history for AD in at least 1 first-degree relative. Much higher concordance of AD exists in monozygotic twins than in dizygotic twins.

Environmental allergens repeatedly have been shown to trigger exacerbations of AD in susceptible individuals. Contact irritants, climate, sweating, aeroallergens, microbial organisms, and stress/psyche are common culprits.

Contact irritants (eg, soaps, solvents, wool clothing, mechanical irritants, detergents, preservatives, perfumes) compromise the integument, creating inflammation, irritation, and a portal of entry for further environmental insult. These surface irritants, along with the macerative effects of sweating and the drying effects of low humidity, lower the pruritic threshold. A vicious cycle of itching and scratching ensues, in which added cutaneous damage caused by scratching further lowers the pruritic threshold and subsequently causes increased itching.

Aeroallergens (eg, house dust mite, molds, pollen, dander) induce peripheral eosinophilia and elevate serum IgE levels. These early effects lead to increased histamine release from IgE-activated mast cells and elevated activity of the T-helper cell–mediated immune system. The increased release of vascular mediators (eg, bradykinin, histamine, slow-reacting substance of anaphylaxis [SRS-A]) induces vasodilation, edema, and urticaria, which in turn stimulate pruritus and inflammatory cutaneous changes.

Microbial agents (e.g.*S. aureus*, *Malassezia* yeasts, *Candida* organisms, *Trichophyton* dermatophytes) act in 2 different ways to promote the flares of AD. The microorganisms directly invade the skin, creating local injury and inflammation, and they induce a systemic allergic response to specific antigens, causing a rise in serum IgE and enhanced activity of the immune system.

Food allergy is implicated in one third to one half of children with AD. The most common food allergens are egg, soy, milk, wheat, fish, shellfish, and peanut, which together account for 90% of food-induced cases of AD in double-blind placebo-controlled food challenges. Fortunately, many food allergies fade in intensity after age 1 year, eliminating the need for long-term restrictive diets.

Stress may trigger AD at the sites of activated cutaneous nerve endings, possibly by the actions of substance P, vasoactive intestinal peptide (VIP), or via the adenyl cyclase–cyclic adenosine monophosphate (cAMP) system.

**History.**Diagnostic criteria for AD have been proposed by Hanifin and Rajka (1980). Appropriate cases must have at least 3 major characteristics and at least 3 minor characteristics.

***Major characteristics include the following***:

– Pruritus
– Typical morphology and distribution (i.e. flexural lichenification and linearity in adults, facial and extensor involvement in infants and young children)
– Chronic or chronically relapsing dermatitis
– Personal or family history of atopy (eg, asthma, allergic rhinoconjunctivitis, AD)

***Minor characteristics are as follows***:

– Xerosis (dry skin)
– Ichthyosis/palmar hyperlinearity/keratosis pilaris
– Hand and/or foot dermatitis
– Cheilitis
– Nipple eczema
– Susceptibility to cutaneous infection (eg, with *Staphylococcus aureus*, herpes simplex virus [HSV], other viruses, warts, molluscum, dermatophytes)
– Erythroderma
– Perifollicular accentuation
– Pityriasis alba
– Early age of onset
– Impaired cell-mediated immunity
– Recurrent conjunctivitis
– Orbital darkening
– Infraorbital fold (e.g. Dennie pleat, Morgan fold)
– Anterior neck folds
– Keratoconus
– Anterior subcapsular cataracts
– Sensitivity to emotional factors
– Food intolerance
– Pruritus with sweating
– Intolerance of wool
– White dermographism
– Immediate type I skin test response
– Elevated total serum IgE
– Peripheral blood eosinophilia

Most atopic children relate a history notable for intense pruritus and dry skin. The quality of the pruritus is referred to as a spreading itch. Affected children often have a lowered itch threshold, resulting in increased levels of cutaneous reactivity in response to stimuli. Patients may succumb to a vicious itch-scratch-itch cycle, in which pruritus stimulates a bout of scratching. This, in turn, increases skin inflammation and triggers a greater sensation of itching, thus exacerbating flares.
Altered cell-mediated immunity has been noted in patients with AD. This is observed clinically as a history of repeated unusual cutaneous infections (e.g. eczema herpeticum, warts, molluscum, dermatophytes).
**Physical:** Three classes of skin lesions exist.

– Acute - Intensely pruritic erythematous papules and vesicles overlying erythematous skin; frequently associated with extensive excoriations and erosions accompanied by serous exudates
– Subacute - Erythema, excoriation, and scaling
– Chronic - Thickened plaques of skin, accentuated skin markings (lichenification), fibrotic papules (prurigo nodularis); possible coexistence of all 3 types of lesions in chronic AD

***Typical locations of lesions by age***.Non-mobile infant - face and scalp. Crawling infant - extensor surfaces of extremities, trunk, face, and neck. Older child and adolescent - wrists, ankles, antecubital fossae, popliteal fossae, and neck. Adult - may be limited to hand and foot eczema.

***Associated findings in AD*** include keratosis pilaris; accentuated palmar creases; lichenification; atopic pleats; allergic shiners; transverse nasal crease; pallor around the nose, mouth, and ears; white dermographism; cataracts; and keratoconus.

Keratosis pilaris, or plucked chicken skin, consists of large cornified plugs in the upper part of hair follicles and produces a stippled appearance of the skin on the outer aspects of the arms and legs and on the buttocks and trunk.

Hyperlinear palms are usually present at birth and persist throughout life. These consist of an increased number of fine lines and accentuated markings on the palms.

Lichenification of the wrists, ankles, popliteal fossae, or antecubital fossae is characteristic of chronic AD. It is observed as thickened, leathery, hyperpigmented patches of skin with a deepening of normal skin creases.

Atopic pleats, also referred to as Morgan-Dennie folds, Morgan folds, Dennie pleats, or mongolian lines, are skin folds observed just below the lower lid of both eyes and are retained throughout life.

Allergic shiners are violet-gray infraorbital discolorations caused by underlying vascular stasis. Increased pressure on nasal and paranasal venous plexuses causes edema in these areas, leading to development of atopic pleats and allergic shiners.

A prominent transverse nasal crease is a common sign of concurrent allergic rhinitis and, along with allergic shiners and atopic pleats, may be a clue to the diagnosis of an atopic diathesis.

***Dermographism*** is a normal reaction in 5% of the population. After a firm pointed instrument is stroked against the skin, the path of the instrument is observed as a red line followed by an erythematous flare that ultimately develops into a wheal. This response occurs within 3 minutes of the insult. White dermographism is a paradoxical reaction wherein the initial red line is replaced within 10 seconds by a white line and an absence of a wheal. This reaction can be observed in AD and allergic contact dermatitis.

Atopic cataracts affect 4-12% of patients with AD and occur much earlier in life than senile cataracts. They typically are bilateral, central, and shield-shaped, and they mature rapidly. Because patients generally are asymptomatic, diagnosis is

usually made by slit lamp examination. Incidence of cataracts in atopic patients appears to be unrelated to the use of topical steroids.

Keratoconus is an elongation of the corneal surface that is thought to be caused by long-term eye rubbing and may be a degenerative change in the cornea. Keratoconus affects approximately 1% of children with AD and generally can be alleviated with the use of contact lenses.

**Complications.**The most common complication of AD is secondary infection.

*Staphylococcus* species and group A beta-hemolytic streptococci are the most frequent organisms cultured from skin lesions. Superinfected eczematoid lesions appear as erythema associated with serous or purulent exudates and crusting. Greasy moist scales on the surface of the lesions and small pustules at the advancing edges may be present. Always consider infection in acute flares of chronic AD or in cases that are unresponsive to appropriate therapy.

Osteomyelitis has been described in patients with superinfected AD. Topical antibiotic therapy is useful for localized infections; however, systemic treatment is preferred for recurrent or widespread infections. The agent of choice is penicillin G if group A streptococci is the known infectious organism. Use erythromycin or a semisynthetic penicillin (e.g. nafcillin, oxacillin, dicloxacillin), if *S. aureus* is a possible cause. Hospitalization and use of intravenous antibiotics are indicated in cases of invasive infection (e.g. osteomyelitis). Perform urinalysis and closely observe patients for symptoms for at least 7 weeks after treatment in endemic areas because systemic antibiotic treatment does not prevent postinfectious glomerulonephritis after a cutaneous infection with nephritogenic M strains of streptococci.

Less commonly, patients with AD may develop an explosive vesicular eruption known as Kaposi varicelliform eruption or eczema herpeticum. Vesicles and pustules typically are umbilicated and initially confined to eczematous skin but may later spread to normal skin. Later in the course of the disease, erosions may be commonplace and confluent, resulting in denuded areas. Tzanck smear of vesicles or a viral culture confirms the diagnosis. Treatment is with acyclovir (if mild, administer 25-30 mg/kg/d, up to 200 mg 5 times per d orally; if severe, administer 5 mg/kg 8h or 1.5 g/$m^2$/d IV).

**Lab Studies:** No definitive laboratory tests to diagnose AD exist. Elevated serum IgE levels and peripheral blood eosinophilia occur in most individuals with AD, and these findings may be useful in confirming the atopic status of suspected cases. The presence of serum IgE directed against the cell wall of *S aureus* is observed in hyper-IgE syndrome and AD. Common infections that mimic or complicate AD can be tested for as follows: conduct a Tzanck smear for HSV, a potassium hydroxide (KOH) preparation for dermatophytes, and a Gram stain for bacterial infections.

**Other Tests.**Prick skin testing to common allergens can help identify specific triggers of AD. For accuracy, antihistamines must be discontinued for 1 week and topical steroids for 2 weeks prior to testing. Although used most often in young children with moderate-to-severe disease, false-negative and false-positive test

results are not uncommon in children younger than 8 years. If positive, these tests do not necessarily indicate clinically significant triggers. Prick skin tests only indicate that the patient has been sensitized to the particular antigens. For example, most children shown to have multiple food allergies by skin tests only demonstrate clinically detectable allergic reactions to 3 or fewer foods when tested by double-blind randomized provocative testing.

Radioallergosorbent test (RAST) and enzyme-linked immunosorbent assay (ELISA) in vitro tests identify serum IgE directed toward specific allergens. As with prick skin tests, these diagnostic methods show a poor predictive value for clinically significant food allergies and may produce false-positive results when the patient's serum contains elevated IgE levels.

**Histologic Findings.** Acute eczematous lesions show histologic markings of hyperkeratosis, parakeratosis, and acanthosis with a decreased or absent granular cell layer. Important features in histologic diagnosis include spongiosis (accumulation of fluid in the intercellular and intracellular areas) and exocytosis (infiltration of leukocytes through the epidermis). Chronic eczematous lesions display hyperkeratosis with areas of parakeratosis and papillomatosis (upward proliferation of dermal papillae).

**Treatment.** The most fundamental and important step in combating AD is rehydration of the stratum corneum. Adequate rehydration preserves the stratum corneum barrier, minimizing the direct effects of irritants and allergens on the skin and maximizing the effect of topically applied therapies, thus decreasing the need for topical steroids.

Lukewarm soaking baths lasting 20-30 minutes are ideal. Very hot water should be avoided to prevent both vasodilation, which can trigger pruritus, and the damage to the skin barrier caused by scalding.

Small amounts of bath oils or emulsification agents may be used for added hydration benefits in older children and adolescents. Bath oils or emulsification agents result in slippery conditions; warn patients and parents of the resultant risks of trauma and drowning after a fall.

Recommended soaps are mild and unscented with a neutral pH. Examples include Dove, Oil of Olay, Caress, Camay, Aveeno, and Purpose. Even these mild soaps are often too drying for atopic skin. If the children are prepubertal, bathing in water alone may be preferable. Postpubertal patients need to use soap in the axillae and groin but do not need it elsewhere.

If soaps are too irritating to the skin, hydrophobic lotions and creams, such as Cetaphil, Diprobase, and Unguentum Merck, may be used. These agents have excellent cleansing properties and low potential for irritation. They should be applied without water and rubbed gently over the skin surface until a light foaming occurs. A soft cotton cloth or tissue can then be applied to wipe away the agent, leaving behind a protective film of stearyl alcohol and propylene glycol.

Baby shampoo may be used to manage scalp dermatitis.Baths should be followed by the immediate application of an occlusive emollient over the entire skin surface

to retain moisture in the epidermis. If an emollient is not applied within 3 minutes of leaving the bath, evaporation causes excess drying of the skin.

Frequently recommended emollients are hydrophobic and ointment-based; these include Vaseline petrolatum jelly, Crisco, vegetable oil, Aquaphor, and Elta. Occasionally, parents may find these agents too greasy for everyday use, and cream-based alternatives may be offered. Common creams are DML Forte, Moisturel, Aveeno, Curel, Purpose, Dermasil, Neutrogena, and Eucerin. This latter group of moisturizers is less effective because of the weaker occlusive effects of creams as compared to ointments; thus, they should be used only if the ointment-based emollients are not well tolerated.

Urea, alpha-hydroxy acid, and lactic acid preparations have also been shown to soften and moisturize dry skin.

For children with repeated cutaneous infections, adding 2 teaspoons of household bleach (eg, Clorox) per gallon of bath water can help reduce incidence of such infections. During acute AD exacerbations, pouring 1 cup of table salt into the bath may ameliorate the stinging effect these children frequently experience while bathing.

Wet dressings are very useful for diverse types of atopic dermatitic flares. They can be used on dry lichenified lesions to improve hydration and increase the penetration of topical corticosteroids; they also work well to dry weeping or oozing lesions via evaporation.

Burow solution 1:40 is a commonly used wet dressing because it is germicidal and directly suppresses weeping lesions by precipitation of protein. Place the dressing over the affected skin site, periodically rewetting the compress. In severe cases, a topical corticosteroid may be applied after the compress for enhanced penetration and action of the medication. A final benefit of wet dressings is to provide a physical barrier against scratching.

Seek psychological counseling, biofeedback, relaxation techniques, massage therapy, and behavioral modifications if emotional stressors are a contributing factor to AD.

Ultraviolet light may benefit some patients. Ultraviolet light in the UVB range may provide control and eliminate or markedly reduce the need for steroids. The new narrow band units are especially effective. Ultraviolet light in the UVA range has been used alone, in combination with oral psoralen administration (PUVA), or with high-dose UVA 1 units. PUVA is not indicated in young patients and may lead to skin cancer with long-term treatments. UVA 1 is an evolving technology that is not yet standardized or readily available enough to recommend. A small number of patients develop erythema or disease flares with light treatment.

Topical corticosteroids are the mainstay of treatment of AD. Topical steroids should be applied only to areas of acute exacerbations, whereas emollients should be used over the remainder of the skin. The absorption of topical steroids is much better through hydrated skin; thus, the ideal time for application is within 3 minutes of taking a bath. Formulations of steroids in ascending order of occlusiveness are lotions, creams, gels, and ointments.

– Lotions contain water and may be drying because of the evaporative effect; thus, they are used mostly in scalp and beard areas where drying effects are not as problematic. Lotions containing alcohol may cause a burning sensation upon application. Lotions may contain preservatives, solubilizers, and fragrances that can irritate the skin.
– Creams generally are tolerated well but are less moisturizing than ointments. Creams are popular for cosmetic appearance and are more convenient during hot weather because they do not occlude eccrine sweat glands as much as ointments and gels. As with lotions, creams may contain preservatives, solubilizers, and fragrances that can irritate the skin.
– Gels are highly occlusive, but the propylene glycol base is irritating to the skin and promotes dryness. Therefore, gels, similar to lotions, are used mostly in scalp and beard areas where the drying effects are not as problematic. They are very effective in the management of acute weeping or vesicular lesions of AD.
– Ointments are the most moisturizing steroid vehicles, but occlusiveness may not be tolerated well because of interference with sweat gland function and resultant development of sweat retention dermatitis, especially in warm humid climates. Ointments work the best on thickened lichenified plaques of AD.

Systemic corticosteroids have been used in severe chronic AD, but usage has been limited in the pediatric population because of the risk of severe adverse effects, including growth retardation and immune suppression.

Pramoxine is a topical antipruritic agent and can be found as Prax, Pramosone, or PrameGel. Oral antihistamines are effective as systemic antipruritics, sedatives, and mild anxiolytics. These are beneficial especially at nighttime because pruritus usually is worse at night. Use diphenhydramine, hydroxyzine, or doxepin.

Coal tar topical preparations have antipruritic and anti-inflammatory effects. They work as disinfectants and astringents and help to correct abnormal keratinization by decreasing both epidermal proliferation and dermal infiltration. They are effective as second-line agents for subacute, chronic, and lichenified AD.

Topically applied tacrolimus has proven to be an effective new therapy for AD. It is a nonsteroidal alternative that is especially useful when treating facial and intertriginous dermatitis. It does not lose efficacy, even after a year of continuous treatment.

Systemic cyclosporine can dramatically reverse severe flares of AD. Because of adverse effects, this treatment should be limited in duration. Once control is obtained, alternative maintenance therapy should be instituted.

Experimental treatments for AD have included trials of gamma-interferon and IL-2; both are inhibitors of Th2-cell functions and have been promising. Oral mycophenolate mofetil, an inhibitor of purine synthesis, has also recently been shown in 2 small series to be an effective alternative form of treatment for severe disease.

*Topical corticosteroids*. In older children and adolescents, treat mild cases of AD with a low-potency (class VI or VII) topical steroid twice a day to decrease inflammation. Examples include hydrocortisone cream or ointment, 1% and 2.5%.

For moderate cases of AD, intermediate-potency steroids (class III, IV, V) may be used for brief periods (<2 weeks) to control an eczematous flare. Subsequently, low-potency steroids can be used to maintain remission.

For severe cases of AD, pulse therapy with high-potency topical steroids (class II) or PO steroids may be beneficial in adolescents. Remember to only use class VII steroids on the face, axillae, groin, and intertriginous areas because of increased absorption. For mild AD in infants, class VI or VII topical steroids should be effective. If the infant has more severe AD, a moderate-potency steroid can be prescribed for up to 1 week and then tapered down to a lower-potency medication for maintenance therapy. In general, do not treat infants with topical steroids in the high-potency classes (class II or above) without a referral to a dermatologist.

*Antimicrobials*. Antistaphylococcal antibiotics (e.g. topical mupirocin or bacitracin, first-generation cephalosporins, macrolides, penicillinase-resistant extended-spectrum penicillins such as oxacillin or dicloxacillin if resistant strains of *S aureus* are encountered, amoxicillin-clavulanate) are helpful in secondary bacterial infections. Herpes simplex superinfections (eczema herpeticum) should be suspected if vesicles are present or if no improvement is observed with PO antibiotics. Tzanck smear of the base of vesicles is positive in 70% of cases. Treat with PO or IV acyclovir for 10 days. Varicella infections may become severe in the setting of AD, and early treatment with acyclovir is recommended. Counsel all children with AD as to the benefits of vaccination against varicella. Treat dermatophyte infections with topical or PO antifungals, such as topical ketoconazole cream or shampoo.

*Immunomodulators*. Topical tacrolimus has been shown to diminish pruritus and inflammation markedly within 3 days of initiating therapy and to have persistent effects after 3 weeks of treatment in adults with moderate-to-severe AD. The only common adverse effect is a local burning sensation upon application.

PO cyclosporine (5 mg/kg/d adult dose) has proven beneficial in patients with severe AD refractory to treatment with topical steroids. Discontinuation of cyclosporine frequently results in rapid relapse of skin disease. Significant adverse effects (eg, nausea, abdominal discomfort, hypertrichosis, paresthesias, hypertension, hyperbilirubinemia, renal impairment) have diminished enthusiasm for this drug.

**Diet.** Earlier claims that breast-feeding may help to prevent AD recently have been modified because of studies depicting no significant difference in the prevalence of AD between breast-fed and formula-fed children. However, a substantial amount of evidence indicates that the child who is breast-fed until age 2 years experiences a delayed age of onset of the disease but that the severity and duration of AD once onset occurs are similar for children in both groups.

Many physicians are currently advocating elimination of specific commonly allergenic foods during the first 1-2 years of life in children with acute AD. The short list includes cow's milk, eggs, tomatoes, citrus fruits, chocolate, wheat products, spiced foods, fish, nuts, and peanut butter. These foods may be reintroduced after controlling the initial acute flare of AD, or parents may elect to

wait until after the child is aged 2 years because food reactivity diminishes markedly with age.

For children older than 5 years, nutritionally adequate elimination diets are the goal if double-blind placebo-controlled trials indicate a clinically significant food allergy. However, most skin tests, RAST, and ELISA tests that reveal positive results against food allergens are not borne out to cause disease flares in clinical trials; thus, elimination diets are only rarely indicated.

Chinese herbal teas have been shown to be efficacious in inducing remission in some children and patients with recalcitrant disease. Because these teas can contain up to 10 different herbs, which have various anti-inflammatory, antihistaminic, or immunosuppressant activities, these effects have not yet been specifically linked to any one ingredient. Reports exist of liver, kidney, and cardiac damage as well as hypersensitivity; thus, risks and benefits need to be further evaluated.

**Activity.** In the subgroup of children with AD who also experience respiratory allergies to animal allergens, parents should consider removing animals from the home or confining them to areas of the house where susceptible children do not come into contact with their dander or saliva.Prohibit smoking in the home and other areas that are frequented by children with allergies.Implement dust mite and mold control measures for allergic children. Counsel parents to use dust mite–proof plastic cases around pillows, mattresses, and box springs. Wash bedding in hot water weekly to remove offending agents. For children who have tested positive for sensitivity to house dust mite by skin test, natamycin spray and benzyl benzoate (Acarosan) may be helpful in controlling mites in carpets and drapes. Avoid irritants that trigger the itch-scratch-itch cycle (e.g, soaps, detergents, chemicals, abrasive clothing, extremes of temperature and humidity).Use pH-neutral minimally defatting soaps (e.g. Dove). Avoid excessive drying of the skin with alcohol-containing astringents. Launder new clothes before wearing to remove manufacturing chemicals. Use liquid detergent rather than powder detergent and add a second rinse cycle to remove all residual detergent. Wear loose fitting open-weave cotton or cotton-blend clothing; avoid wool. Use a humidifier in the winter to prevent excessive skin dryness and an air conditioner in the summer to prevent sweating and associated macerative effects on the skin. Decreased humidity indoors helps prevent the growth of mold.

**Prevention.** Prevention of acute flares and the subsequent development of chronic lesions of AD are indicators of successful treatment for this disease. Maintenance of adequate hydration of the stratum corneum, avoidance of known or probable allergens and irritants, rapid self-treatment with the proper class of topical steroids, and judicious use of complementary therapies (eg, antipruritics, stress relievers, antibiotics) are the cornerstones of ensuring a high quality of life unimpeded by the more severe aspects of this disease.

**Prognosis:** Twenty to 40% of atopic children remain atopic as adults. Many children outgrow severe AD and only experience itchy or inflamed skin if exposed to exogenous irritants as adults.

## 7.2. Contact Dermatitis, Allergic

**Synonyms and related keywords:** contact hypersensitivity

**Background:** The term contact dermatitis sometimes is used incorrectly as a synonym for allergic contact dermatitis (ACD). Contact dermatitis is inflammation of the skin induced by chemicals that directly damage the skin and by specific sensitivity in the case of ACD. ACD is inflammation of the skin manifested by varying degrees of erythema, edema, and vesiculation. It is a delayed type of induced sensitivity (allergy) resulting from cutaneous contact with a specific allergen to which the patient has developed a specific sensitivity.

**Pathophysiology:** Most chemicals able to provoke ACD have small molecules (<500 d). Approximately 3000 chemicals are well documented as specific causes of ACD. The small chemical molecules responsible for ACD must bind to carrier proteins on Langerhans cells, which are situated within the suprabasilar layer of the epidermis. Langerhans cells are the antigen-presenting cells within the skin. Langerhans cells interact with $CD4^+$ T cells (helper T cells).

Cytokines also play an important role in ACD because they regulate accessory-adhesion molecules, such as intercellular adhesion molecule 1. Interleukin 8 may be a cytokine indicating ACD, not irritant contact dermatitis. Langerhans cells can migrate from the epidermis to the regional draining lymph nodes. Sensitization to a chemical requires intact lymphatic pathways. The initial sensitization typically takes 10-14 days from initial exposure to a strong contact allergen such as poison ivy. Some individuals develop specific sensitivity to allergens (eg, chromate in cement) following years of chronic low-grade exposure associated with chronic irritant contact dermatitis resulting from the alkaline nature of cement. Once an individual is sensitized to a chemical, ACD develops within hours to several days of exposure. $CD4^+$ $CCR10^+$ memory T cells persist in the dermis after ACD clinically resolves.

**Age:** ACD may occur in neonates. In elderly individuals, the development of ACD may be delayed somewhat, but the dermatitis may be more persistent once developed.

**Causes:** Approximately 25 chemicals appear to be responsible for as many as one half of all cases of ACD.

– Poison ivy is the classic example of acute ACD. ACD from poison ivy is characterized by linear streaks of acute dermatitis that develop where plant parts have been in direct contact with the skin.

– Nickel is the leading cause of ACD in the world. ACD to nickel typically is manifested by dermatitis at the sites where earrings or necklaces containing nickel are worn or where metal objects containing nickel are in contact with the skin. Nickel may be considered a possible occupational allergen. Workers in whom nickel may be an occupational allergen primarily include hairdressers, retail clerks, caterers, domestic cleaners, and metalworkers. Individuals allergic to nickel

occasionally may develop vesicles on the sides of the fingers (dyshidrotic hand eczema or pompholyx) from nickel in the diet.

– Allergy to 1 or more chemicals in rubber gloves is suggested in any individual with chronic hand dermatitis who is wearing them, unless patch testing demonstrates otherwise. ACD to chemicals in rubber gloves typically occurs maximally on the dorsal aspects of the hand. Usually, a cutoff of dermatitis occurs on the forearms where skin is no longer in contact with the gloves. Individuals allergic to chemicals in rubber gloves may develop dermatitis from other exposures to the chemicals (e.g. under elastic waistbands).

– Individuals allergic to dyes and permanent press and wash-and-wear chemicals added to textiles typically develop dermatitis on the trunk, which occurs maximally on the lateral sides of the trunk but spares the vault of the axillae. Primary lesions may be small follicular papules or may be extensive plaques. Individuals in whom this ACD is suggested should be tested with a series of textile chemicals, particularly if routine patch testing reveals no allergy to formaldehyde. New clothing is most likely to provoke ACD, since most allergens decrease in concentration in clothing following repeated washings.

– Preservative chemicals added to cosmetics, moisturizers, and topical medications are major causes of ACD. The most widely used preservatives include parabens, which are not a frequent cause of ACD despite their wide use. The risk of ACD appears to be highest to quaternium-15, followed by ACD to isothiazolinones (Kathon CG).

– Formaldehyde is a major cause of ACD. Certain preservative chemicals widely used in shampoos, lotions, other moisturizers, and cosmetics are termed formaldehyde releasers.

– Individuals may develop allergy to fragrances. Fragrances are found not only in perfumes, colognes, aftershaves, deodorants, and soaps, but also in numerous other products, often as a mask to camouflage an unpleasant odor. Unscented products may contain fragrance chemicals used as a component of the product and not labeled as fragrance. Individuals allergic to fragrances should use fragrance-free products. Unfortunately, the exact chemicals responsible for a fragrance in a product are not labeled. Four thousand different fragrance molecules are available to formulate perfumes. The fragrance industry is not required to release the names of ingredients used to compose a fragrance, even when individuals develop ACD to fragrances found in topical medications. Deodorants may be the most common cause of ACD to fragrances because they are applied to occlude skin..

– Massage and physical therapists and geriatric nurses are at higher risk of occupational ACD to fragrances.

– In the last decade, it has become clear that many individuals with chronic dermatitis develop allergy to topical corticosteroids. Most affected individuals can be treated with some topical corticosteroids, but an individual can be allergic to all topical and systemic corticosteroids. Budesonide and tixocortol pivalate are useful

patch test corticosteroids for identifying individuals allergic to topical corticosteroids.

– The risk of allergy to neomycin is related directly to the extent of its use in a population. The risk of allergy to neomycin is much higher when it is used to treat chronic stasis dermatitis than when it is used as a topical antibiotic on cuts and abrasions in children. Assume that individuals allergic to neomycin are allergic to chemically related aminoglycoside antibiotics (e.g. gentamicin, tobramycin). Avoid these drugs both topically and systemically in individuals allergic to neomycin.

– Avoid topical use of benzocaine. Benzocaine is included in most standard patch test trays. Individuals allergic to benzocaine may safely use or be injected with Xylocaine, which does not cross-react with benzocaine.

– Many individuals complain of adverse reactions to sunscreens, but many of these individuals are not allergic to the sunscreen materials. They may be allergic to preservatives in these products or may have nonspecific cutaneous irritation from these products.

– Occasionally, individuals develop photo ACD. ACD may be accentuated by ultraviolet (UV) light, or patients may develop an allergic reaction only when a chemical is present on the skin and when the skin is exposed sufficiently to ultraviolet light A (UV-A; 320-400 nm).

**History.**A detailed history, both before and after patch testing, is crucial in evaluating individuals with ACD. Potential causes of ACD and the materials to which individuals are exposed should be patch tested. Patients with ACD require a much more detailed history compared to those with most other dermatologic disorders.

History is equally important after patch testing. Only history and questioning can determine whether the materials to which a patient is allergic are partly or wholly responsible for the current dermatitis. A positive patch reaction may indicate only sensitivity and not the cause of current dermatitis.

***Preexisting skin diseases.*** Individuals with stasis dermatitis are at high risk for developing ACD to materials and agents applied to the areas of stasis dermatitis and leg ulcers. Neomycin is an important cause of ACD in these individuals because it is used frequently despite the lack of documentation of its efficacy in the treatment of stasis ulcers. Individuals with otitis externa frequently are allergic to topical neomycin and topical corticosteroids. Individuals with pruritus ani and pruritus vulvae may become sensitized to benzocaine and other medications applied to chronic pruritic processes. Women with lichen sclerosus et atrophicus frequently develop ACD, complicating the severe chronic vulvar dermatosis. Patch testing these patients may provide important information that can help in the management of recalcitrant and difficult-to-manage dermatosis.

***Atopic dermatitis.*** Patients with a history of atopic dermatitis are at increased risk for developing nonspecific hand dermatitis and irritant contact dermatitis. Patients with a history of atopic dermatitis do not appear to be at an increased risk for ACD, despite the wide range of topical medications and moisturizers used by

individuals with chronic atopic dermatitis. Patients with atopic dermatitis are at lower risk of ACD to poison ivy. Some European studies indicate that patients with atopic dermatitis may have increased incidence of ACD to nickel.

***Onset of symptoms.*** Individuals with ACD typically develop dermatitis (within a few days of exposure) in areas that were exposed directly to the allergen. Certain allergens (eg, neomycin) penetrate intact skin poorly, and the onset of dermatitis may be delayed up to a week following exposure.A minimum of 10 days is required for individuals to develop specific sensitivity to a new contactant. An individual who never has been sensitized to poison ivy may develop only a mild dermatitis 2 weeks following the initial exposure but typically develops severe dermatitis within 1-2 days of the second and subsequent exposures. Remember that removing the poison ivy allergen from the skin is difficult, and unless an individual washes exposed skin within 30 minutes of exposure, ACD will develop. The hallmark of the diagnosis of poison ivy is linear dermatitic lesions.

The possibility of an external cause of dermatitis always must be considered if the dermatitis is linear or sharply defined. The immediate onset of dermatitis following initial exposure to material suggests either a cross-sensitization reaction, prior forgotten exposure to the substance, or nonspecific irritant contact dermatitis provoked by the agent in question.

***Eyelid dermatitis***. Individuals may develop dermatitis on eyelids and other exposed skin following exposure to airborne allergens.

***Contact urticarial.*** Immediate reactions, i.e. visible lesions developing less than 30 minutes after exposure, indicate contact urticaria (not ACD), particularly if urticarial in appearance and if associated with other symptoms such as distant urticaria, wheezing, ophthalmedema, rhinorrhea, or anaphylaxis.

Rubber latex currently is the most important source of allergic contact urticaria. The term hypoallergenic may refer to gloves that do not contain sensitizing chemicals added to rubber latex but may not indicate whether the gloves are rubber latex free. Some individuals may have delayed specific contact sensitivity to rubber latex, but contact urticaria to rubber latex is much more common than ACD to latex. Individuals with hand dermatitis, hospital workers, children with spina bifida, and atopic individuals are at increased risk of developing contact urticaria to rubber latex. Individuals may have ACD to chemicals added to rubber gloves and have contact urticaria to latex. Individuals wearing rubber gloves should be evaluated carefully for both possibilities.

Rare reports exist of immediate anaphylactic reactions to topical antibiotics (e.g. bacitracin).

***Occupational dermatitis***. Contact dermatitis is 1 of the 10 leading occupational illnesses. It may prevent individuals from working. The hands are the sites exposed most intensely to contact allergens and irritants, both at work and at home. The hands are crucial for performing many work-related tasks. ACD in response to workplace materials may improve initially on weekends and during holidays, but individuals with chronic dermatitis may not demonstrate the classic history of weekend and holiday improvement. Irritant contact dermatitis is more likely if

multiple workers are affected in the workplace. Most allergens rarely sensitize a high percentage of the population.

***Hobbies***. Hobbies may be the source of ACD, eg, woodworking with exotic tropical woods or processing film using color-developing chemicals that may provoke cutaneous lesions of lichen planus from direct skin exposure.

***Medications***. Self-prescribed and physician-prescribed medications are important causes of ACD. The workplace nurse may dispense ineffective and sensitizing topical preparations, such as Merthiolate, which may change a simple abrasion into a severe case of ACD. Individuals may develop allergy to preservatives in medications and/or to the active ingredients in topical medications, especially neomycin and topical corticosteroids.

***Iatrogenic adverse effects***. Chronic use of systemic corticosteroids to treat ACD may produce severe morbidity. Individuals with ACD should not receive chronic systemic corticosteroids or immunosuppressives, unless extensive patch testing and evaluation have failed to identify remedial causes of the severe dermatitis. Chronic widespread use of potent topical corticosteroids may produce local skin atrophy and systemic adverse effects.

**Physical.**Acute ACD is characterized by pruritic papules and vesicles on an erythematous base. Lichenified pruritic plaques may manifest chronic ACD. Occasionally, ACD may affect the entire integument (i.e. erythroderma, exfoliative dermatitis). The initial site of dermatitis often provides the best clue regarding the potential cause of ACD.

Hands. Hands are an important site of ACD, particularly in the workplace. Common causes of allergic dermatitis on the hands include the chemicals in rubber gloves.

Perianal. ACD is frequent in the perianal area as a result of the use of sensitizing medications and remedies (eg, topical benzocaine).

Otitis externa. Topical medications are important causes of ACD in cases of otitis externa.

Airborne ACD. Chemicals in the air may produce airborne ACD. This dermatitis usually occurs maximally on the eyelids, but it may affect other areas exposed to chemicals in the air, particularly the head and the neck.

Ophthalmologic. Allergy to chemicals in ophthalmologic preparations may provoke dermatitis around the eyes.

Hair dyes. Individuals allergic to hair dyes typically develop the most severe dermatitis on the ears and adjoining face rather than on the scalp.

Stasis dermatitis and stasis ulcers. Individuals with stasis dermatitis and stasis ulcers are at high risk for developing ACD to topical medications applied to inflamed or ulcerated skin. The chronicity of this condition and the frequent occlusion of applied medications contribute to the high risk of ACD to medicament (e.g. neomycin) in these patients. Individuals may develop widespread dermatitis from topical medications applied to leg ulcers or from cross-reacting systemic medications administered intravenously. For example, a patient allergic to

neomycin may develop systemic contact dermatitis if treated with intravenous gentamicin.

Erythema multiforme. Erythema multiforme (EM) is a severe cutaneous reaction with targetoid lesions that occurs primarily after exposure to certain medications or is triggered by infection, most commonly by herpes simplex virus. Rare cases of EM have been reported after ACD resulting from exposure to poison ivy, tropical woods, nickel, and hair dye.

**Complications.**Occasionally, ACD is complicated by secondary bacterial infection, which may be treated by the appropriate systemic antibiotic.Darkly pigmented individuals may develop areas of hyperpigmentation or hypopigmentation from ACD. Occasionally, they may develop depigmentation at sites of ACD to certain chemicals.

**Lab Studies:** Potassium hydroxide preparation and/or fungal culture to exclude tinea are often indicated for dermatitis of the hands and feet.

**Procedures.*Patch testing.*** Patch testing is required to identify the external chemicals to which the person is allergic. The greatest quality-of-life benefits from patch testing occur in patients with recurrent or chronic ACD. Patch testing is most cost effective and reduces the cost of therapy in patients with severe ACD.Patch testing must be performed by health care providers trained in the proper technique. Most dermatologists can perform patch testing using the TRUE test (consult the *Physicians' Desk Reference*), which can identify relevant allergies in as many as one half of affected patients. More extensive patch testing is indicated to identify allergies to chemicals not found in the TRUE test. Such testing typically is available only in a limited number of dermatology offices and clinics.Individuals with suspected ACD without positive reactions on the TRUE test or with chronic dermatitis or relapsing dermatitis, despite avoiding chemicals to which they are allergic (identified on TRUE test), need additional patch testing. Many individuals have more than 1 contact allergy and may be allergic to 1 or more chemicals found on the TRUE test and on special allergen trays or series. Testing to more allergens increases accuracy of the diagnosis of ACD. Selection of allergens for testing requires consideration of the patient's history and access to appropriate environmental contactants.

Certain chemicals (e.g. neomycin) typically produce delayed positive patch test reactions at 4 days or later following initial application. A tendency exists for elderly patients to manifest positive patch test reactions later than younger patients. Do not perform patch testing on patients taking more than 15 mg per day of prednisone. Oral antihistamines may be used during the patch test period if required.

Angry back syndrome or excited skin syndrome: If a patient has a large number of positive patch test reactions, retesting the patient sequentially to a small series of these allergens may be necessary to exclude nonspecific false-positive reactions. The syndrome most likely occurs in individuals who have active dermatitis at the time of patch testing or who have a strong positive patch test reaction, both of

which may induce local skin hyperreactivity in the area where patches were applied.

– ***Repeat open application test***. For individuals who develop weak or 1+ positive reactions to a chemical, the repeat open application test (ROAT) is useful in determining whether the reaction is significant. ROAT is most useful when an individual has a 1+ reaction to a chemical found in a leave-on consumer product. For example, an individual with a weak reaction to a preservative found in a moisturizer may apply the moisturizer twice a day for a week to the side of the neck or behind an ear. If the individual applies it twice a day for a week without developing clinical dermatitis, the 1+ reaction likely was not meaningful. Conversely, if the individual develops dermatitis following a few days of repeated application of the suspected product, then the weak patch test reaction is highly relevant.

– ***Dimethylgloxime test***. The dimethylgloxime test is a useful and practical way to identify metallic objects that contain enough nickel to provoke allergic dermatitis in individuals allergic to nickel. Dermatology staff may test suspected metal products in the office, or the individual may purchase a test kit and test objects at home or at work, particularly jewelry or metallic surfaces. Other chemical tests are available for other suspected allergens (eg, formaldehyde, chromate). Occasionally, chemical analyses may be necessary to determine whether a material contains a suspected allergen or to identify new unknown allergens.

***Skin biopsy*** may help exclude other disorders, particularly tinea, psoriasis, and cutaneous lymphoma. Skin biopsy of skin lesions of the palms and soles has several potential pitfalls, which include the following: the stratum corneum and epidermis are particularly thick on the palms and soles. This makes the histologic diagnosis of psoriasis more difficult and increases the possibility that the biopsy specimen will lack sufficient dermis for optimal diagnosis.

An overly deep skin biopsy of the thenar area can cut the motor nerve, which is the recurrent branch of the median nerve. A biopsy from the sole may leave a chronic painful scar on which the patient must walk.

**Histologic Findings.**Histology of ACD is similar to that found in other forms of eczematous dermatitis. A pattern of subacute chronic dermatitis or acute dermatitis may be seen. The inflammatory infiltrate in the dermis predominately contains lymphocytes and other mononuclear cells. Epidermal edema (i.e. spongiosis and microvesicle formation) may be seen, but these changes may be absent in long-standing dermatitis in which thickening of the epidermis (acanthosis) with hyperkeratosis and parakeratosis may be seen in the epidermis and stratum corneum. ACD is provokes atypical T-cell infiltrates, simulating mycosis fungoides.

**Medical Care.**The cause of ACD must be identified; otherwise, the patient is at increased risk for chronic or recurrent dermatitis.

The goal of pharmacotherapy is to reduce morbidity and to prevent complications. Topical glucocorticosteroids are the mainstay of therapy. When choosing a topical

glucocorticosteroid, match the potency to the location of the dermatitis and the vehicle to the morphology (ointment for dry scaling lesions; lotion or cream for weeping areas of dermatitis).

For severe acute ACD (e.g. rhus dermatitis, erythroderma), systemic glucocorticosteroids or other immunosuppressive medications may be needed.

In some cases, ACD may prove persistent despite avoidance of the allergen. In some of these cases (eg, nickel), ingestion of minute amounts of the allergen is believed to drive the process, and chelation therapy with disulfiram can be beneficial. In other instances, the cause of persistence remains enigmatic; many allergens penetrate through rubber gloves. PUVA can be helpful in these cases.

***Symptomatic treatment.*** Cool compresses with saline or aluminum acetate solution are helpful for acute vesicular dermatitis (e.g. poison ivy). Some individuals with widespread vesicular dermatitis may obtain relief from lukewarm oatmeal baths. Sedating oral antihistamines may help diminish pruritus. Patients should avoid using topical antihistamines, including topical doxepin, because of the apparently high risk of iatrogenic ACD to these agents.

***Corticosteroids.*** Topical corticosteroids are the mainstay of treatment, with the strength of the topical corticosteroid appropriate to the body site. For severe ACD of the hands, 3-week courses of class I topical corticosteroids are required, while class 6 or class 7 topical corticosteroids typically are used for ACD of intertriginous areas. Acute severe ACD, such as acute severe ACD to poison ivy, often needs to be treated with a 2-week course of systemic corticosteroids. Most adults require an initial dose of 40-60 mg. The oral corticosteroid is tapered over a 2-week period, but a complicated tapering regimen probably is not necessary given the short duration of systemic corticosteroids. The systemic corticosteroids must be administered for 2 weeks, because shorter courses are notorious for allowing poison ivy dermatitis to relapse. Long-acting triamcinolone acetonide (Kenalog) 40-60 mg may be used in place of oral prednisone in these cases.

***Topical immunomodulators***. Topical immunomodulators (TIMs) are approved for atopic dermatitis and are prescribed for cases of ACD when they offer safety advantages over topical corticosteroids. TIMs do not cause cutaneous atrophy or glaucoma or cataracts when applied near the eye. Pimecrolimus (Elidel cream) is a topical treatment often helpful for ACD of the face. Tacrolimus (Protopic 0.1% ointment) appears to be the most helpful TIM for ACD of the hands.

***Psoralen plus UV-A***. Individuals with chronic ACD that is not controlled well by topical corticosteroids may benefit from psoralen plus UV-A (PUVA) treatments.

***Immunosuppressive agents***. Rarely, chronic immunosuppressive agents, such as azathioprine (Imuran) or cyclosporine (Neoral), are used in recalcitrant cases of severe chronic widespread ACD or severe hand dermatitis that prevents the individual from working or performing daily activities. Biologicals active on T cells may be helpful in the future.

***Disulfiram***. Occasionally, an individual who is highly allergic to nickel with severe vesicular hand dermatitis benefits from treatment with disulfiram (Antabuse). The chelating effect of disulfiram is helpful in reducing the body's

nickel burden. Alcohol ingestion may produce severe adverse reactions in patients taking disulfiram.

**Consultations.**Many primary care physicians treat individuals with typical poison ivy dermatitis who respond well to a 2-week treatment course using topical or systemic corticosteroids and subsequently avoid poison ivy and related plants. Acute dermatitis that resolves with short-term treatment does not require further evaluation. Individuals with chronic dermatitis, particularly if it possibly is related to work, require detailed history and patch testing to standard screening sets and additional allergens as indicated by history, occupation, hobbies, and results on initial patch testing.

**Diet.**Some chemicals tested by the TRUE test may be present in the diet. Individuals with severe dermatitis, particularly if it is a disabling vesicular dermatitis of the hands, may be treated with diets low in minerals and chemicals to which the individual is allergic. A low-nickel diet is the most common, but published diets are available that are low in chromate, cobalt, or balsam of Peru. These diets may be attempted for the occasional allergic patient with severe chronic vesicular dermatitis.

**Activity.**Individuals with severe acute ACD may be incapacitated temporarily and unable to work. Most individuals with ACD may require light duties or restrictions of duties. They should avoid further contact with the chemicals to which they are allergic or chemicals that cross-react with these materials. Patients also should minimize exposure to irritant chemicals, particularly if the dermatitis is active or recently resolved. They should use mild cleansing agents on the skin, such as Aquanil, Cetaphil cleanser, or Oilatum-AD, and should apply bland protective emollients, such as SBR Lipocream, Cetaphil cream or Neutrogena hand cream, to help minimize relapse of ACD or development of irritant contact dermatitis of ceramide cream (e.g. Impruv).

**Prevention.** To prevent recurrence of ACD, instruct patients thoroughly concerning allergen(s) and the types of products likely to contain allergen(s). For many patients with allergic reactions to fragrances, preservatives, vehicles, and medicaments, reading cosmetic labels and package inserts of topical/systemic medicaments may be sufficient to avoid allergens. For patients allergic to nickel, the dimethylgloxime test can alert them the presence of the metal. For many other patients with allergic reactions to chemicals that are unlikely to be labeled on consumer products (e.g. rubber accelerators), suitable allergen alternatives (e.g. gloves specifically known to be accelerator free) must be provided by the practitioner.Many cases of ACD, especially of the hands, occur in the occupational setting. Proper worker education and hygiene may prevent allergic reactions. For example, glutaraldehyde is a known sensitizer with widespread use as a cold sterilizing agent in medicine and dentistry. Needless cases of ACD to this biocide occur because of the lack of proper education regarding the appropriate use of gloves and other barriers to cutaneous contact.Advise patients to avoid identified chemicals to which they are allergic to minimize the risk of relapse, the risk of chronic contact dermatitis, and the risk of adverse effects from chronic use of

nonspecific suppressive treatments (eg, topical and systemic corticosteroids, cyclosporine).

**Prognosis.** Individuals with ACD may have persistent or relapsing dermatitis, particularly if the material(s) to which they are allergic is not identified or if they continue to practice skin care that is no longer appropriate (i.e. they continue to use harsh chemicals to wash their skin, they do not apply bland emollients to protect their skin).The longer an individual has severe dermatitis, the longer it is believed it will take the dermatitis to resolve once the cause is identified.Some individuals have persistent dermatitis following ACD, which appears to be true especially in individuals allergic to chrome.A particular problem is neurodermatitis (lichen simplex chronicus), in which individuals repeatedly rub or scratch an area initially affected by ACD.

## 7.3. Contact Dermatitis, Irritant

**Synonyms and related keywords:** non-allergic contact dermatitis, ICD

**Background:** Irritant contact dermatitis (ICD) is inflammation of the skin typically manifested by erythema, mild edema, and scaling. ICD is a nonspecific response of the skin to direct chemical damage that releases mediators of inflammation predominately from epidermal cells. A corrosive agent causes the immediate death of epidermal cells as manifested by chemical burns and cutaneous ulcers.

ICD remains understudied compared to allergic contact dermatitis. Most articles on contact dermatitis concern allergic contact dermatitis. This largely reflects the fact that with patch testing, a specific hypersensitivity and a probable cause of dermatitis can be identified in most cases of allergic contact dermatitis. No diagnostic test exists for ICD. The diagnosis rests on the exclusion of other cutaneous diseases (especially allergic contact dermatitis) and on the clinical appearance of dermatitis at a site sufficiently exposed to a known cutaneous irritant.

In the consumer world, the term hypoallergenic is used widely, although no Food and Drug Administration–approved definition of hypoallergenic exists. A necessity exists for hypoirritating cleansers, cosmetics, moisturizers, and protectants; however, no standard method exists to identify products that are of great use to individuals with susceptible skin (e.g. atopic dermatitis, facial skin of individuals with rosacea).

The hands are the most important sites of ICD. Most occupational skin disorders are ICD resulting from repeated workplace exposure of the hands to soaps, cleansers, and solvents.

**Pathophysiology.**A wide range of chemicals with sufficient concentration or duration of exposures are capable of acting as cutaneous irritants. Common cutaneous irritants include detergent and water. Most cases of housewife's eczema

are ICD resulting from repeated skin exposure to low-grade cutaneous irritants, particularly soaps, water, and detergents.
Cumulative ICD from repeated mild skin irritation from soap and water is common. For example, hand-washing frequency of more than 35 times per shift was associated strongly with occupational hand dermatitis in intensive care unit workers (odds ratio=4.13).
Solvents are another major cause of cutaneous irritation because they remove essential fats and oils from the skin, which increases transepidermal water loss and renders the skin susceptible to the increased direct toxic effects of other previously well-tolerated cutaneous exposures.
Microtrauma also may produce skin irritation. A common example is fiberglass, which may produce pruritus with minimal visible inflammation in susceptible individuals. Many plant leaves and stems bear small spicules and barbs that produce direct skin trauma.
Skin irritation predisposes the skin to develop sensitization to topical agents. An exacerbation of ICD may reflect development of allergic contact dermatitis to topical creams, medications, or rubber gloves.
The pathogenesis of ICD involves resident epidermal cells, dermal fibroblasts, endothelial cells, and various leukocytes interacting with each other under the control of a network of cytokines and lipid mediators. Keratinocytes play an important role in the initiation and perpetuation of skin inflammatory reactions through the release of and responses to cytokines. Resting keratinocytes produce some cytokines constitutively.
A variety of environmental stimuli (eg, ultraviolet light, chemical agents) can induce epidermal keratinocytes to release inflammatory cytokines (interleukin 1, tumor necrosis factor alpha), chemotactic cytokines (interleukin 8, interleukin 10), growth promoting cytokines (interleukin 6, interleukin 7, interleukin 15, granulocyte-macrophage colony-stimulating factor, transforming growth factor), and cytokines regulating humoral versus cellular immunity (interleukin 10, interleukin 12, interleukin 18). Intercellular adhesion molecule 1 promotes the infiltration of leukocytes into the epidermis in cutaneous inflammatory reactions, including ICD.
Significantly increased numbers of dividing keratinocytes are present 48 and 96 hours after exposure to the anionic emulsifying agent sodium lauryl sulfate (used in medicated shampoos, skin cleansers, acne treatments, and toothpastes and as an experimental irritant).
All irritants provoke a similar pattern of cellular infiltration in the dermis; the densities of most of the cell types rise in proportion to the intensity of inflammation. Within the epidermis, marked differences exist in the patterns of cellular infiltration among different irritants.
**Causes.**Almost any material may be a cutaneous irritant with sufficient exposure in time and/or concentration.

*Dry air*. Dry air renders the skin more susceptible to cutaneous irritants. Sufficiently dry air alone may provoke ICD. Most cases of winter itch are a result of dry skin from the drier air found during sustained periods of cold weather.
*Water*. Continual exposure to water may produce maceration or repeated evaporation of water from the skin may produce cutaneous irritation by desiccation of the skin. Even distilled water experimentally provokes increased $CD11c^+$ cells and neutrophils in the epidermis.
*Solvents*. Many individuals are exposed to solvents, particularly at work. Solvents such as alcohol or xylene remove lipids from the skin, producing direct ICD and rendering the skin more susceptible to other cutaneous irritants, such as soap and water.
*Alcohol*. ICD from alcohol most often is cumulative. Manual workers may wash their hands inappropriately with solvents to remove oil, grease, paints, or other materials; thus, they develop ICD. Inappropriate skin cleansing is a primary cause of ICD in the workplace. Washing facilities and methods must be inspected when investigating the workplace for 1 or more cases of occupational ICD. The irritating agents include aromatic, aliphatic, and chlorinated solvents, as well as solvents such as turpentine, alcohol, esters, and ketones. Some organic solvents produce an immediate erythematous reaction on the skin and remove lipids from the stratum corneum.
*Metalworking fluids*. Neat oils most commonly produce folliculitis and acne. They may cause ICD (but rarely allergic dermatitis). Water-based metalworking fluids often cause ICD in exposed workers; surfactants in these fluids are the main culprit.
*Cumulative ICD*. This is common in many occupations that often are termed wet work. Health care workers wash their hands 20-40 times a day, producing cumulative ICD. Similar exposures occur among individuals who wash hair repeatedly or in cleaners or kitchen workers.
*Microtrauma*. Many plant leaves and stems bear small spicules and barbs that produce direct skin trauma.
*Fiberglass*. Fiberglass produces direct damage to the skin, usually manifested by pruritus that may result in excoriation and secondary skin damage. Cutaneous irritation primarily is caused by fiberglass with diameters exceeding 4.5 □m. Controversy surrounds whether individuals with dermatographism are more susceptible to fiberglass dermatitis. Most workers with ICD resulting from fiberglass develop hardening, in which they tolerate further cutaneous exposure to fiberglass.
*Mechanical trauma*. Pressure produces callus formation. Pounding produces petechia or ecchymosis. Sudden trauma or friction produces blistering in the epidermis. Repeated rubbing or scratching produces lichenification.
*Rubber gloves*. Some rubber gloves may provoke direct cutaneous irritation. Many workers complain of irritation from the powder in rubber gloves. Remember that gloves compromised by a hole may allow an irritant to enter; occlusion dramatically increases skin damage from the irritant. Occlusion accentuates the

effects, good or bad, of topical agents. Kerosene may produce skin changes similar to that of toxic epidermal necrolysis following occluded cutaneous exposure. Excessive amounts of ethylene oxide in surgical sheets also may produce similar changes.

*Sodium lauryl sulfate*. This chemical is found in some topical medications, particularly acne medications, and also is a classic experimental cutaneous irritant.

*Hydrofluoric acid.* A hydrofluoric acid burn is a medical emergency. Remember that onset of clinical manifestations may be delayed after the acute exposure (crucial to diagnosis). Unfortunately, hydrofluoric acid burns are most frequent on the digits where the pain is most severe and management is most difficult.

*Alkalis*. Skin surfaces normally have an acidic pH and alkalis (eg, many soaps) produce more irritation than many acids.

**History.**A detailed history is required because the diagnosis of ICD rests on the history of exposure of the affected body site to the cutaneous irritant. Patch testing also is used in severe or persistent cases to exclude allergic contact dermatitis as a component of the individual's cutaneous manifestations.

***Primary subjective symptoms include the following***. History of sufficient exposure to a cutaneous irritant is noted. Onset of symptoms occurs within minutes to hours of exposure in simple acute ICD. The onset of signs and symptoms may be delayed by weeks in cumulative ICD.Pain, burning, stinging, or discomfort exceeding pruritus early in the clinical course occur.

***Less important subjective criteria include the following***. Onset of dermatitis within 2 weeks of exposure. Reports of many other coworkers or family members affected. Occupational ICD typically affects workers who are new to a job, who are constitutionally more susceptible to ICD, or who have not learned to protect their skin from cutaneous irritants.

Individuals with history of atopic dermatitis (especially of the hands) are more susceptible to ICD, particularly of the hands.

Other causes of contact dermatitis (particularly allergic contact dermatitis) must be excluded by history and/or patch testing to the relevant allergens.

**Physical.** Proposed the **primary diagnostic criteria for ICD** as follows:

Macular erythema, hyperkeratosis, or fissuring predominating over vesiculation

Glazed, parched, or scalded appearance of the epidermis

Healing process beginning promptly on withdrawal of exposure to the offending agent

Patch testing negative and includes all possible allergens

***Minor objective criteria*** include the following:

Sharp circumscription of the dermatitis

Evidence of gravitational influence such as a dripping effect

Lower tendency for the dermatitis to spread than in cases of allergic contact dermatitis

Morphologic changes suggesting small differences in concentration or contact time producing large differences in skin damage

***Other criteria*** include the following:

ICD may be manifested by vesicles, particularly on the hands.
Dyshidrotic eczema or pompholyx is a morphologic term describing deep-seated vesicles on the sides of the fingers and, to a lesser extent, on the palms. The identical morphology may be produced by contact allergens. ICD has much less tendency to form vesicles.
Individuals may develop a habit of continuing to rub a site initially affected by ICD and may develop secondary neurodermatitis or lichen simplex chronicus (lichenification), which may be accepted as a sequela of an occupational injury.
**Complications.** ICD increases the risk of sensitization to topical medications. Skin lesions may become colonized secondarily and/or infected, particularly by *Staphylococcus aureus*.Secondary neurodermatitis (lichen simplex chronicus) may develop in individuals with ICD, particularly in those with workplace exposures or under psychologic stress.Postinflammatory hyperpigmentation or hypopigmentation may occur in areas affected by ICD or persist after resolution of ICD in individuals with more pigmented skin.Scarring may occur after corrosive agent exposure, excoriation, or artifact, causing ulceration.
**Lab Studies.** A bacterial culture can be obtained in cases complicated by secondary bacterial infection.A KOH examination may be performed and samples for mycology may be obtained to exclude superficial tinea infections or candidal infections, depending on site and morphology of lesions.Findings of significantly elevated serum immunoglobulin E occasionally are useful to substantiate an atopic diathesis in the absence of a personal or family history of atopy.
**Procedures.** Patch testing can be performed to diagnose contact allergies, but no patch test exists that proves that a cutaneous irritant is responsible for a particular case of ICD. Diagnosis rests on exclusion of allergic contact dermatitis and history of sufficient exposure to a cutaneous irritant.Skin biopsy can help exclude other disorders, such as tinea, psoriasis, or cutaneous T-cell lymphoma. All clinical cases of dermatitis are similar histologically. Skin biopsy of skin lesions of the palms and soles has several potential pitfalls. The stratum corneum and epidermis are particularly thick on the palms and soles. This makes the histologic diagnosis of psoriasis more difficult and increases the possibility that the biopsy specimen lacks sufficient dermis for optimal diagnosis. An overly deep skin biopsy of the thenar area can cut the motor nerve, which is the recurrent branch of the median nerve. A biopsy from the sole may leave a chronic painful scar on which the patient must walk.
**Histologic Findings:** The histopathology of acute experimental ICD has been studied to a greater extent than chronic ICD, which is the primary clinical complaint. Cellular changes seen in the skin vary according to the chemical nature and concentration of the irritant applied, duration of exposure, severity of ensuing response, and time of sampling for acute ICD. Many primary irritants cause overt necrosis if applied in a sufficiently high concentration for sufficient time.
Most histologic examinations of ICD reveal some degree of intercellular edema or spongiosis in the epidermis. Spongiosis usually is less pronounced than that seen in allergic contact dermatitis reactions. Parakeratosis also is observed widely in ICD

reactions. The histology of chronic ICD is one of hyperkeratosis with areas of parakeratosis, moderate-to-marked epidermal hyperplasia (acanthosis), and elongation of the rete ridges.

**Consultations.**Multidisciplinary consultations may be required when many workers become affected with ICD in a workplace. Identifying and remediating the causes of widespread ICD interfering with workplace productivity and worker quality of life is important.Any patient with hydrofluoric acid burn should be evaluated as a medical emergency by a physician experienced in the management of hydrofluoric exposures and burns. Consider regional intravenous infusion of calcium gluconate as a therapeutic option in hydrofluoric acid burns to forearm, hand, or digits when topical therapy fails.

**Further Outpatient Care.**Individuals with ICD frequently are seen, particularly from the workplace. Identifying and minimizing exposure to cutaneous irritants at home and work is crucial.Advise individuals to use bland emollients after washing hands with soap and before sleep. Recommend mild skin cleansers (eg, Aquanil, Cetaphil cleanser, Oilatum AD, Neutrogena cleanser) in place of soap on affected areas.Instruct individuals to refrain from the use of inappropriate solvents (eg, gasoline) or abrasives (eg, pumice stone) to cleanse hands; these directly defat or traumatize the skin.

ICD does not respond as well to topical corticosteroids as allergic contact dermatitis, probably because the clinical pathophysiology often is different.

ICD often responds better to treatment with bland topical steroid preparations (eg, fluocinolone or amcinonide ointment) rather than products such as Diprolene cream (betamethasone valerate in an augmented base containing propylene glycol). Propylene glycol is a rare allergen but a frequent cutaneous irritant, especially when the skin is more susceptible to irritants.

**Prognosis.** Prognosis is good for nonatopic individuals in whom ICD is diagnosed and managed promptly.Individuals with atopic dermatitis remain highly susceptible to ICD and may find that the tasks of many common occupations (e.g. nursing, hairdressing) produce too much direct skin inflammation to continue with these careers.

## 7. 4. Drug Eruptions

**Synonyms and related keywords:** adverse cutaneous drug reactions, cutaneous reaction to drugs, drug-induced cutaneous reactions, mucocutaneous drug reactions

**Background:** Drug eruptions can mimic a wide range of dermatoses. The morphologies are myriad and include morbilliform, urticarial, papulosquamous, pustular, and bullous. Medications can also cause pruritus and dysesthesia without an obvious eruption.

A drug-induced reaction should be considered in any patient who is taking medications and who suddenly develops a symmetric cutaneous eruption. Medications that are known for causing cutaneous reactions include antimicrobial

agents, non-steroidal anti-inflammatory drugs (NSAIDs), cytokines, chemotherapeutic agents, anticonvulsants, and psychotropic agents.

Prompt identification and withdrawal of the offending agent may help limit the toxic effects associated with the drug. The decision to discontinue a potentially vital drug often presents a dilemma.

**Pathophysiology:** Drug eruptions may be divided into immunologically and non-immunologically mediated reactions.

**Immunologically mediated reactions**

Coombs and Gell proposed 4 types of immunologically mediated reactions, as follows:

- **Type I** is immunoglobulin E (IgE)–dependent reactions, which result in urticaria, angioedema, and anaphylaxis.
- **Type II** is cytotoxic reactions, which result in hemolysis and purpura.
- **Type III** is immune complex reactions, which result in vasculitis, serum sickness, and urticaria.
- **Type IV** is delayed-type reactions with cell-mediated hypersensitivity, which result in contact dermatitis, exanthematous reactions, and photoallergic reactions.

Insulin and other proteins are associated with type I reactions. Penicillin, cephalosporins, sulfonamides, and rifampin are known to cause type II reactions. Quinine, salicylates, chlorpromazine, and sulfonamides can cause type III reactions. Type IV reactions, the most common mechanism of drug eruptions, are often encountered in cases of contact hypersensitivity to topical medications, such as neomycin. Sulfonamides are most frequently associated with toxic epidermal necrolysis (TEN).

Although most drug eruptions are type IV hypersensitivity reactions, only a minority is IgE-dependent. That is, antibodies can be demonstrated in fewer than 5% of cutaneous drug reactions. Type IV cell-mediated reactions are not dose dependent, they usually begin 7-20 days after medication, they may involve blood or tissue eosinophilia, and they may recur if drugs chemically related to the causative agent are administered.

**Non-immunologically mediated reactions**

Non-immunologically mediated reactions may be classified according to the following features: accumulation, adverse effects, and direct release of mast cell mediators, idiosyncratic reactions, intolerance, Jarisch-Herxheimer phenomenon, overdosage, or phototoxic dermatitis. (Symptoms of Jarisch-Herxheimer reactions disappear with continued therapy. Drug therapy should be continued until the infection is fully eradicated.)

An example of accumulation is argyria (blue-gray discoloration of skin and nails) observed with use of silver nitrate nasal sprays.

Adverse effects are normal but unwanted effects of a drug. For example, antimetabolite chemotherapeutic agents, such as cyclophosphamide, are associated with hair loss.

The direct release of mast cell mediators is a dose-dependent phenomenon that does not involve antibodies. For example, aspirin and other NSAIDs cause a shift in leukotriene production, which triggers the release of histamine and other mast cell mediators. Radiographic contrast material, alcohol, cytokines, opiates, cimetidine, quinine, hydralazine, atropine, vancomycin, and tubocurarine also may cause release of mast-cell mediators.

Idiosyncratic reactions are unpredictable and not explained by the pharmacologic properties of the drug. An example is the individual with infectious mononucleosis who develops a rash when given ampicillin.

Imbalance of endogenous flora may occur when antimicrobial agents preferentially suppress the growth of one species of microbe, allowing other species to grow vigorously. For example, candidiasis frequently occurs with antibiotic therapy.

Intolerance may occur in patients with altered metabolism. For example, individuals who are slow acetylators of the enzyme *N*-acetyltransferase are more likely than others to develop drug-induced lupus in response to procainamide.

Jarisch-Herxheimer phenomenon is a reaction due to bacterial endotoxins and microbial antigens that are liberated by the destruction of microorganisms. The reaction is characterized by fever, tender lymphadenopathy, arthralgias, transient macular or urticarial eruptions, and exacerbation of preexisting cutaneous lesions. The reaction is not an indication to stop treatment because symptoms resolve with continued therapy. This reaction can be seen with penicillin therapy for syphilis, griseofulvin or ketoconazole therapy for dermatophyte infections, and diethylcarbamazine therapy for oncocerciasis.

Overdosage is an exaggerated response to an increased amount of a medication. For example, increased doses of anticoagulants may result in purpura.

Phototoxic dermatitis is exaggerated sunburn response caused by the formation of toxic photoproducts, such as free radicals or reactive oxygen species.

**Mortality/Morbidity:** Most drug eruptions are mild, self-limited and usually resolve after the offending agent has been discontinued. Severe and potentially life-threatening eruptions occur in approximately 1 in 1000 hospital patients. Mortality rates for erythema multiforme (EM) major are significantly higher. Stevens-Johnson syndrome (SJS) has a mortality rate below 5%, whereas the rate for TEN approaches 20-30%; most patients die from sepsis.

**History:** The first step is to review the patient's complete medication list, including over-the-counter supplements. Document any history of previous adverse reactions to drugs or foods. Consider alternative etiologies, especially viral exanthems and bacterial infections. Exanthematous eruptions in children are more likely to be due to a viral infection than another infection; however, most such reactions in adults are due to medications.

Note any concurrent infections, metabolic disorders, or immunocompromise (e.g., due to HIV infection, cancer, chemotherapy) because these increase the risk of drug eruptions. Immunocompromised persons have a 10-fold higher risk of developing a drug eruption than the general population. Although HIV infection causes profound anergy to other immune stimuli, the frequency of drug

hypersensitivity reactions, including severe reactions (e.g., TEN), is markedly increased in HIV-positive individuals. Patients with advanced HIV infection (CD4 count <200 cells/μL) have a 10- to 50-fold increased risk of developing an exanthemata's eruption to sulfamethoxazole.

Note and detail the following:

– All prescription and over-the-counter drugs including topical agents, vitamins, and herbal and homeopathic remedies
– The interval between the introduction of a drug and onset of the eruption
– Route, dose, duration, and frequency of drug administration
– Parenterally administered drugs, which are more likely than oral agents to cause anaphylaxis
– Topically applied drugs, which are more likely than other drugs to induce delayed-type hypersensitivity reactions
– Multiple courses of therapy and prolonged administration of a drug, which can cause allergic sensitization
– Any improvement after drug withdrawal and any reaction with re-administration

**Physical:** Although most drug eruptions are exanthematous, different types of drug eruptions exist. With every drug eruption, it is important to evaluate for certain clinical features that may indicate a severe potentially life-threatening drug reaction, such as TEN or hypersensitivity syndrome. Such features include the following: mucous membrane erosions, blisters (blisters herald a severe drug eruption), Nikolsky sign (epidermis sloughs off with lateral pressure), confluent erythema, angioedema and tongue swelling, palpable purpura, skin necrosis, lymphadenopathy, high fever, dyspnea, or hypotension

Appreciating the morphology and features of drug eruptions is important. This can help the clinician determine the causative medication and the most appropriate treatment.

Acneiform - inflammatory papules or pustules that have a follicular pattern; localized primarily on the upper body; in contrast to acne vulgaris, comedones are absent in acneiform eruptions.

Acral erythema (erythrodysesthesia) - relatively common reaction to chemotherapy characterized by symmetric tenderness, edema, and erythema of the palms and soles; thought to be a direct toxic effect on the skin; often resolves 2-4 weeks after chemotherapy is discontinued.

Acute generalized exanthematous pustulosis (AGEP) - acute-onset fever and generalized scarlatiniform erythema with many small, sterile, nonfollicular pustules; clinical presentation is similar to pustular psoriasis, but AGEP has more marked hyperleukocytosis with neutrophilia and eosinophilia; most cases are caused by drugs (primarily antibiotics) often in the first few days of administration; a few cases are caused by viral infections, mercury exposure, or UV radiation; resolves spontaneously and rapidly, with fever and pustules lasting 7-10 days then desquamation over a few days.

Dermatomyositis-like - cutaneous findings of dermatomyositis (e.g., Gottron papules), but patients tend to lack muscle involvement, associated malignancy, and antinuclear antibodies; improvement is usually noted after the drug is withdrawn
EM - includes a spectrum of diseases, e.g., EM minor and EM major; many categorize SJS and TEN as EM major and differentiate them by body-surface involvement.
EM minor - overall, a mild disease; patients are healthy; characterized by target lesions distributed predominantly on the extremities; mucous membrane involvement may occur but is not severe; patients with EM minor recover fully, but relapses are common; most cases are due to infection with herpes simplex virus, and treatment and prophylaxis with acyclovir is helpful.
SJS - characterized by widespread skin involvement, large and atypical targetoid lesions, significant mucous membrane involvement, constitutional symptoms, and sloughing of 10% of the skin; may be caused by drugs and infections (especially those due to *Mycoplasma pneumoniae*).
SJS/TEN overlap - epidermal detachment involves between 10-30% of body surface area.
TEN - severe skin reaction; prodrome of painful skin (not unlike sunburn) quickly followed by rapid, widespread, full-thickness skin sloughing; affects 30% or more the total body surface area; secondary infection and sepsis are major concerns; pneumonia may develop due to aspiration of sloughed mucosa; most cases are due to drugs; the risk of TEN in HIV-positive patients is 1000-fold higher than the general population.
Erythema nodosum - tender, red, subcutaneous nodules, typically on the anterior aspect of the legs; lesions do not suppurate or become ulcerated; a reactive process often secondary to infection, but it may be due to medications, especially oral contraceptives and sulfonamides.
Erythroderma - widespread inflammation of the skin; may result from an underlying skin condition, drug eruption, internal malignancy, or immunodeficiency syndrome; lymphadenopathy is often noted, and hepatosplenomegaly, leukocytosis, eosinophilia, and anemia may be present
Fixed drug eruptions - lesions recur in the same area when the offending drug is given; circular, violaceous, edematous plaques that resolve with macular hyperpigmentation is a characteristic; lesions occur 30 minutes to 8 hours after drug administration; perioral and periorbital lesions may occur, but the hands, feet, and genitalia are the most common locations
Hypersensitivity syndrome - potentially life-threatening complex of symptoms often caused by anticonvulsants; patients have fever, sore throat, skin rash, lymphadenopathy, hepatitis, nephritis, and leukocytosis with eosinophilia; usually begins within 1-3 weeks after new drug is started, but it may develop 3 months or later into therapy; aromatic anticonvulsant drugs cross-react (phenytoin, phenobarbital, carbamazepine); valproic acid is a safe alternative.
Leukocytoclastic vasculitis - most common severe drug eruption seen in clinical practice; blanching erythematous macules quickly followed by palpable purpura;

fever, myalgias, arthritis, and abdominal pain may be present; typically appears 7-21 days after the onset of drug therapy; laboratory evaluation to exclude internal involvement is mandatory.
Lichenoid - appears similar to lichen planus and may be severely pruritic; eruption may include eczematous or psoriasiform papules.
Lupus - drug-induced systemic lupus erythematosus (SLE), which produces symptoms identical to those of SLE with skin findings being uncommon, or drug-induced subacute cutaneous lupus erythematosus (SCLE), which is characterized by an– annular psoriasiform, non-scarring lesions in a photodistributed pattern
Morbilliform or exanthematous - the most common pattern of drug eruptions, quintessential drug rash; exanthem is typically symmetric, with confluent erythematous macules and papules that spare the palms and soles; typically develops within 2 weeks after the onset of therapy.
Pseudoporphyria - largely a drug-induced condition, but it can also occur with use of tanning beds and hemodialysis; patients have blistering and skin fragility that is clinically and pathologically identical to that of porphyria cutanea tarda, but hypertrichosis and sclerodermoid changes are absent, and urine and serum porphyrin levels are normal; treatment is sun protection and withdrawal of medication.
Serum sickness and serum sickness–like - type III hypersensitivity reaction mediated by the deposition of immune complexes in small vessels, activation of complement, and recruitment of granulocytes; cutaneous signs typically begin with erythema on the sides of fingers, hands, and toes and progress to a widespread eruption (most often morbilliform or urticarial); viscera may be involved, and fever, arthralgia, and arthritis are common; serum sickness–like reaction has a clinical presentation similar to that of serum sickness, without the immune complex deposition; renal involvement is rare; serum sickness–like reactions usually occur antibiotic therapy, especially with cefaclor.
Sweet syndrome (acute febrile neutrophilic dermatosis) - tender, erythematous, papules and plaques most often on the face, neck, upper trunk, and extremities; surface of lesions may become vesicular or pustular; systemic findings are common and include fever (most often), arthritis, arthralgias, conjunctivitis, episcleritis, and oral ulcers; laboratory evaluation usually reveals elevated sedimentation rate, neutrophilia, and leukocytosis; Sweet often occurs in association with cancers, inflammatory disorders, pregnancy, and medication.
Urticarial - usually occurs as small wheals that may coalesce or that may have cyclical or gyrate forms; lesions usually appear shortly after the start of drug therapy and resolve rapidly when the drug is withdrawn; giant urticaria easily mistaken for EM.
Vesiculobullous - can resemble pemphigus, bullous pemphigoid, linear IgA dermatosis, dermatitis herpetiformis, herpes gestationis, or cicatricial pemphigoid; most causative drugs have a thiol group, disulfide bonds, or sulfur-containing rings that are metabolized to thiol forms; thiol-induced pemphigus tends to resemble pemphigus foliaceus or pemphigus erythematosus; non-thiol eruptions may

resemble pemphigus vulgaris or pemphigus vegetans; mucosal findings may be most common with non-thiol drugs; direct and indirect immunofluorescence may be positive in drug-induced pemphigus and bullous pemphigoid; eruptions usually resolve after the inducing drug is discontinued, but D-penicillamine–induced pemphigus may take months to resolve and corticosteroids are often needed.

**Lab Studies.**History and physical examination are often sufficient for diagnosing mild asymptomatic eruptions.Severe or persistent eruptions may require further diagnostic testing. Biopsy can be helpful in confirming the diagnosis of a drug eruption (e.g., by showing eosinophils in morbilliform eruptions or numerous neutrophils without vasculitis in Sweet syndrome).CBC count with differential may show leukopenia, thrombocytopenia, and eosinophilia in patients with serious drug eruptions.Serum chemistries may be useful. Liver involvement leading to death can occur in hypersensitivity syndromes. Special attention should be paid to the electrolyte balance and renal and/or hepatic function indices in patients with severe reactions, such as SJS, TEN, or vasculitis.Antibody and/or immunoserology tests may be ordered. Antihistone antibodies are noted in drug-induced SLE, whereas anti-Ro/SS-A antibodies are most common in drug-induced SCLE.Direct cultures may be needed to investigate a primary infectious etiology or secondary infection.Urinalysis, stool guaiac tests, and chest radiography are important for patients with vasculitis.

**Imaging Studies.**Chest radiography, along with urinalysis and stool guaiac tests, is important for patients with vasculitis.

**Other Tests.**Rechallenge tests by means of skin prick or patch testing to confirm the causative agent is of limited value.Skin tests may be hazardous to patients who have had severe reactions. With the possible exception of AGEP, patch tests have a low sensitivity and specificity and are not useful.

**Histologic Findings.**In some cases, biopsy may be helpful in establishing a diagnosis of a drug reaction. Histopathology of an exanthematous drug eruption may show both superficial and deep perivascular inflammatory cell infiltrates. Eosinophils in the infiltrate suggest such a drug eruption.In patients with Sweet syndrome, biopsy reveals edema of the superficial dermis and a dense infiltrate of neutrophils. Leukocytoclasia may be present, but vasculitis is absent. Histopathology of TEN shows subepidermal split, full-thickness epidermal necrosis and a sparse perivascular lymphocytic infiltrate.

**Medical Care.**The ultimate goal is always to discontinue the offending medication if possible. Individuals with drug eruptions are often the most ill patients taking the most medications, many of which are essential for their survival. However, all nonessential medications should be limited. Once the offending drug has been identified, it should be discontinued promptly. Knowledge of the common eruption inducing-medications may help in identifying the offending drug.It is possible to treat the patient through morbilliform eruptions (i.e., continue medication even in patients with a rash). The eruption often resolve, especially if the individual is being treated with antihistamines. Most believe that exanthematous drug eruptions are not a precursor to severe reactions, such as TEN. Nevertheless, all patients with

severe morbilliform eruptions should be monitored for mucus-membrane lesions, blistering, and skin sloughing.

Treatment of a drug eruption depends on the specific type of reaction. Therapy for exanthematous drug eruptions is supportive. First generation antihistamines are used around the clock. Mild topical steroids (hydrocortisone or desonide) and moisturizing lotions are also used, especially during the late desquamative phase.

Severe reactions, such as SJS, TEN, and hypersensitivity reactions, warrant hospital admission. TEN is best managed in a burn unit with special attention given to electrolyte balance and signs of secondary infection. Because adhesions can develop and result in blindness, ophthalmologic evaluation is mandatory. Also, there is mounting evidence that intravenous Ig (IVIG) may improve outcomes for TEN patients.

Hypersensitivity syndrome, a systemic reaction characterized by fever, sore throat, skin rash and internal organ involvement, is potentially life threatening. Timely recognition of the syndrome and immediate discontinuation of the anticonvulsant or other offending drug is crucial. Patients may require liver transplantation if the drug is not stopped in time. Treatment with systemic corticosteroids has been advocated.

Therapy for most drug eruptions is mainly supportive. Morbilliform eruptions are treated with oral antihistamines and topical steroids. IVIG may be an effective treatment for TEN. Prednisone may be used in the treatment of hypersensitivity syndrome with heart and lung involvement, severe serum sickness–like reaction, and Sweet syndrome.

**Prognosis.** Full recovery without any complications is expected for most drug eruptions. Even after the responsible agent is discontinued, drug eruptions may clear slowly or worsen over the next few days. The time required for total clearing may be 1-2 weeks or longer.Patients with exanthematous eruptions should be counseled to expect mild desquamation as the rash resolves.Patients with hypersensitivity syndrome are at risk of becoming hypothyroid, usually within the first 4-12 weeks after the reaction.The prognosis for patients with TEN is guarded. Scarring, blindness, and death are possible.

## 7.5. Urticaria

Urticaria is characterized by transient itchy pale dermal swellings secondary to the release of histamine and possibly other vasoactive agents from mast cells.

**ETIOLOGY.** The release of histamine and possibly other vasoactive mediators from mast cells leads to a sudden increase in vascular permeability allowing the escape of fluid from the circulation into the tissues. Mast cells may degranulate in response to a number of stimuli including physical, chemical, pharmacological and immunological.

Different mechanisms may be operating in different types of urticaria. The type I hypersensitivity is mediated through the IgE attached to the mast cell which will degranulate on exposure to the specific antigen. Patients suffering from this type of allergic urticaria frequently have a personal or family history of atopy.

Mast cells can also degranulate by other non - immunological stimuli. Certain drugs, for example morphine, codeine, ethanol, polymyxin B, and bacterial, plant or intervertebrate toxins can stimulate mast cells to degranulate directly.

Other drugs like salicylates and NSAIDs, on the other hand, act on the must cell through its action on the cyclo-oxygenase pathway. It has been postulated that food additives such as tartazine, azo dyes, benzoates and sulphites can provoke urticaria through a similar mechanism.

Recently some research workers have demonstrated the presence of IgG auto-antibodies directed against IgE receptor Fc epsilon RI of mast cells and basophils in some patients with chronic idiopathic urticaria, which can activate the mast cells to degranulate. This autoimmune hypothesis of idiopathic chronic urticaria has led to the use of various immune therapies for treatment of the condition.

Vasodilatation, dermal edema and a mild perivascular infiltration of lymphocytes and eosinophils are seen in a typical lesion of urticaria. However in a small number of patients repeated biopsies may show a predominance of neutrophils and eosinophils infiltrate and absence of endothelial damage, representing a late phase reaction. This picture would suggest that other cellular elements and mediators may operate in the pathogenesis of urticaria in some cases.

### CLASSIFICATION OF URTICARIA

Various types of classification exist; the following classification adopts a more practical approach (see Box 7.1)

## Box7.1 Clinical Classification of Urticaria and Angioedema

**Ordinary urticaria**
- Acute (up to 6 weeks of continuous activity)
- Chronic (6 weeks or more of continuous activity)
- Episodic (intermittent)

**Physical urticaria** (reproducibly induced by the same physical stimulus)
- Aquagenic urticaria
- Cholinergic urticaria
- Cold urticaria
- Delayed pressure urticaria
- Dermographism
- Localized heat urticaria
- Solar urticaria
- Vibratory angioedema

**Angioedema** (without wheals)
**Contact urticaria** (induced by biological or chemical skin contact)
**Urticarial vasculatis** (defined by vasculitis on skin biopsy)

## Table7.1 Common Causesof Urticaria

| | |
|---|---|
| **Drugs** | Salicylates, penicillin, ACE inhibitors, NDSAID, allopurinol and many others |
| **Foods** | Fish, nuts, egg, strawberries, milk, cheese, wine and may others |
| **Food additives** | Azo dyes, benzoates, sulphites and yeast |
| **Infections** | Hepatitis B, infectious mononucleosis, candidosis and focal sepsis |
| **Inhalants** | Grass pollens, moulds, housedust mites, etc. |
| **Infestation** | Enterobius, filariasis, ascariasis |
| **Immune complex** | Transfusion reaction, drugs |

## CLINICAL FEATURES

The lesions in urticaria are usually not difficult to recognize. They are intensely itchy, with a white palpable center of edema and a variable halo of erythema. The size and shape can be highly variable and individual lesions usually last for several hours except in urticarial vasculitis and angioedema where the lesion may persist longer. Frequently patients do not have any lesion during the visit to the clinic and one hat to rely on the description from the patient to diagnose a prior attack of urticaria.

The history is very important for the diagnosis of different types of urticaria in particular for physical urticaria. The frequency, duration, severity, and timing of the attacks may give clues to the diagnosis and are essential; for subsequent management. A thorough food and drug history should be elicited. The characteristic rash of physical urticaria,if present on examination, together with the typical history would usually allow the diagnosis to be made. In case of doubt, simple tests can be done to confirm the diagnosis (Table 7.2).

After making the diagnosis, one should always try to look out for any underlying causes and associated involvements. Focal sepsis, such as dental abscess and

urinary tract infectionhave been reported to cause chronic urticaria. Urticaria can also be the presenting symptom of connective tissue diseases and other features of the disease would usually be evident. Acute urticaria can be just part of the manifestation of serum sickness with systemic symptoms like fever, arthritis and nephritis. Similarly systemic symptoms are also seen in patients with urticarial vasculitis.

**Table7.2 Tests for Physical Urticaria**

| | |
|---|---|
| Cholinergic urticaria | Exercise test, whole body warming |
| Dermographism | Light stroke on the skin, dermographometer |
| Cold urticarial | Ice cube test |
| Solar urticarial | Phototesting |
| Aquagenic | Water at $25^{o}$ C compresses |

## INVESTIGATION

In most patients suffering from urticaria, the correct diagnosis can be made after history taking and physical examination. A complete blood counts and ESR is adequate for the majority who has no other abnormal physical finding. Other investigations should be done when necessary.

1) complete blood count and ESR:look for eosinophilia
2) liver function test
3) complement C3 and C4
4) C1 esterase inhibitor level
5) investigation underlying infections: chest radiograph, urine for culture, stool for ova, throat swab, HbsAg, viral study etc.
6) ANF, RF etc. In suspected connective tissue disease
7) Skin biopsy: urticarial vasculitis, urticaria pigmentosa
8) RAST: controversial as to its usefulness
9) Skin prick test: useful for contact urticaria. Difficult to interpret for chronic idiopathic urticaria

### Acute Urticaria

The cause of the cute attack is often obvious and there may be a history of similar attack. Initial investigations should include the differential white cell count and ESR measurement. The presence of eosinophilia points to parasitic infestation. Other possible causative factors listed above should be sought for.

Since the casual factor can usually be withdrawn, subsequent attack can be avoided ad long-termed treatment is usually not required. Challenge test is not advisable since acute urticaria is frequently IgE mediated and there is a definite risk of anaphylaxis during the test. Though the prognosis is good in most cases, those with persistent symptoms for weeks may actually be suffering from chronic idiopathic urticaria with an acute onset.

Most of these acute episodes can be successfully controlled with antihistamine. In acute urticaria of serum sickness type hypersensitivity, a short course of systemic

steroid may be necessary. Parenteral adrenaline is lifesaving in case of anaphylaxis and bronchial constriction. Resuscitation procedures should be carries out as indicated.

**Chronic Idiopathicurticaria**

Chronic idiopathic urticaria is defined as urticaria lasting longer than 6 weeks, for which no obvious cause can be found. This is the commonest type of urticaria in a dermatology clinic. Although symptomatic relief can be achieved with drug therapy, a certain percentage of patients may suffer from continuous symptoms for years without true emission.

Numerous factors have been suggested for causing this disease including sea food, azo dyes, food preservatives, candida in their gut and trace of penicillin in dairy product. Some patients may benefit from elimination of one of these factors, but for most others the cause of the disease remains obscure. Recently autoimmune etiology has also been proposed.

By definition, no obvious etiological factor is apparent and special investigations are nearly always unhelpful. For most patients with chronic idiopathic urticaria, a complete blood count, ESR for screening may be adequate. Stool for ova is indicated if there is eosinophilia. Other tests detailed above should be performed for individual patient as directed by the history and examination. Prick test and intradermal skin test are often positive but are difficult to interpret. Challenge tests with food coloring agents and preservatives, if available, are helpful in the management.

Although no underlying cause can be found, for the majority of patients their symptoms can be well controlled by drug with minimal disturbance to their daily life. Depending on the patient's tolerance, a sedating or non-sedatingantihistamine can be prescribed during daytime. Because most patients have more severe attack at night time, an additional nocturnal dose of mere sedating drug like promethazine is helpful. The patient should be encouraged to keep a food diary. Food containing tartrazine dye and preservatives as well as drugs that known to aggravate urticaria should be avoided. In suitable cases, elimination diet can be carried out with the help of a dietitian.

Tolerance to antihistamine therapy may develop in a patient whose symptoms are previously under control. This tolerance cannot be overcome by increasing the dosage or by changing to another antihistamine. The cause of tolerance is thought to be due to the down regulation of the H1 receptors. Ketotifen and sodium cromoglycate can be tried and responsiveness to antihistamine may return. Hospital admission may be required for alternative therapy in different cases.

**Cholinergic Urticaria**

A common condition in young adults with intensely itchy and short-lived eruption developing in response to sweating, exercise, emotion and hot foods. It is postulated that an increase in blood temperature triggers a neural reflex which releases acetylcholine from sympathetic nerve endings, in turn activate the mast

cell to degranulate. Characteristic small wheals, less than 2 mm in diameter with surrounding red halo are more profuse on the upper trunk and proximal parts of the upper limbs. Thus it is also called micropapular urticaria. Associated systemic symptoms include faintness, headache, wheezing and palpitation.
Diagnosis is established from the history and the findings of characteristic rash during an attack. The rash can also be brought up on exercise or whole body warming. These lesions can often be reproduced by intradermal injection of cholinergic drugs, e.g., metholyl or acetylcholine.
Treatment is unsatisfactory. Patients, especially those with associated systemic symptoms, should be told to avoid situations that can precipitate an attack. Some patients improve with antihistamine therapy. This can be taken regularly or at times when they anticipate attacks. Fortunately for most patients the condition tends to improve spontaneously.

**Pressure Urticaria**
This rather rare condition is not a true urticaria. Delayed cutaneous erythema and edema and subcutaneous edema occur in response to the sustained application of pressure to the skin. The lesions itch and burn. They appear between 30 min to 9 hours after the stimulus. A large proportion of these patients have associated chronic idiopathic urticaria.
The lesions characteristically occur after certain activities: sitting on hard chairs, carrying bags, leaning against furniture, wearing seat belts and lying on hard mattresses. Swelling of the feet and hands, often indistinguishable from angioedema occurs after walking, jogging, running, climbing ladder and using a screwdriver. During severe attacks, arthralgia and a flu-like illness may accompany the rash.
The pathogenesis of pressure urticaria is not known. Histamine is probably not an important mediator of this disease and treatment with antihistamine is useless. Other forms of treatment including the use of NSAIDs and colchicine have been tried with varying results. Systemic steroid is an effective agent bit is limited by its side effects.

**Symptomatic Dermographism**
Dermographism means whealing after direct pressure on the skin. The patient notices that the skin itches with linear wheals appearing after scratching. The itching and whealing reach their maximum in 5-10 minutes after the stimulus and disappear 30-60 minutes later. It is an exaggerated response of the skin to trauma.
Lesions frequently appear in areas where clothing is tight and at sites of scratching. Patients can be of any age group but young adults are more often affected. No associated systemic disease has been recognized and no increased incidence in patients with chronic idiopathic urticaria is noted. The diagnosis can be confirmed by using the more sophisticated dermographometer. Any patient who itches and wheals at or below a stroking pressure of $3.5 \times 10^5$ Pa has symptomatic

dermographism. The tendency to dermographism may last for years but ultimately improve in most cases,

**Solar Urticaria**

Solar urticaria is a rare photodermatosis of unknown etiology. It is occasionally associated with polymorphic light eruption, other urticarias, lymphocytoma cutis or lupus erythematosus. It may also be systematic of porphyria cutanea tarda.

Patients notice erythema, burning and urticarial wheals within minutes following exposure to sunlight or other visible light source. Wheals can develop anywhere on the body, mostly in the sun exposed skin. If the whole body is irradiated, severe generalized solar urticaria can occur with hemodynamic disturbance. The action spectrum of solar urticaria is broad, ranging from UVC, UVB, and UVA to visible spectrum. The diagnosis can be confirmed by phototesting with monochromator on areas of the body that are normally covered e.g. the buttock. If monochromator is not available, lesions of solar urticaria can be reproduced outdoor by direct exposure to sunlight or visible light.

Avoidance of sunlight is essential in the management. The body should be covered with clothing and the patient should be advised to use an appropriate sunscreen. Antihistamines can produce symptomatic relief. Other treatment modalities that have been used include hardening with UVB, UVA, or visible light, PUVA, and plasmapheresis.

**Cold Urticaria**

Patients with cold urticaria develop whealing on exposure to cold. Wheals typically appear on exposed areas on a cold day. Handling of cold objects also causes immediate local reaction. There may be swelling of the mouth and esophagus after drinking cold water. If whealing is extensive, cold urticaria may be associated with systemic symptoms like faintness, wheezing and palpitations. Diagnosis is established by placing an ice cube (wrapped in plastic bag) on the skin for 30 seconds to 10 minutes. Wheals form on rewarming. In some cases, water at $7^{o}C$ is more effective in bringing out the wheal.

It is important to warn patients against swimming in cold water or immersing in cold water as syncope may occur. Antihistamine treatment is partially effective in suppressing symptoms. Cyprohepatidine is generally considered to be the drug of choice. Salbutamol and aminophylline can relieve the pruritus of cold urticaria. Unlike antihistamines these drugs act by suppressing histamine release from skin mast cells. Doxepin and ketotifen may also be useful.

Desensitization to cold has a place in the management of this condition. This should be carried out in the hospital under antihistamine cover. The procedure begins with putting one limb in water at $15^{o}C$ for 5 min, hourly at first and then at longer intervals up to 24 hours. Other limbs and the face can then be treated. The exposure needs to be repeated indefinitely at 24 hours intervals to maintain the effect.

It should be remembered that occasionally cold urticaria is secondary to the presence of cryoglobulin, cold hemolysin and cryofibrinogen in the circulation.

**Aquagenic Urticaria**

This is a rare type of physical urticaria in which brief contact of the skin with water of any temperature causes an immediate urticaria eruption at the site of contact, the morphology of which closely resembles that of cholinergic urticaria. This condition may persist for many years. Acquagenic pruritus is a related but distinct condition in which brief contact of skin with water evokes intense local pruritus without any skin lesion. Patients with this disorder, which is probably quite common in the elderly, are often wrongly labelled as psychoneurosis or senile pruritus. Complete blood count should be checked as this condition may be symptomatic of polycythemia rubra vera. Both disorders involve histamine release from skin mast cells and respond well to antihistamine. UVB therapy is also helpful.

**Vibratory Angioedema**

Vibratory angioedema is an acute short-lived itchy swelling of the skin that occurs within minutes of application of a vibratory stimulus to the skin. This condition is rare and is probably genetically transmitted. It is benign and the familiar form is not associated with any other physical urticaria. Affected patients generally limit their activities to avoid symptoms. The lesions tend to appear after low frequencies vibration (about 10 Hz) like handling a power lawn mower and running, and wheals can be seen within minutes after the stimulus and disappear within an hour. Clapping and riding a motor bike may also produce lesions. The severity of symptoms is proportional to the intensity of the provoking stimulus. If the stimulus is sufficiently strong, facial and/or generalized erythema may occur. Systemic symptoms like headache and dizziness are also reported. Treatment with antihistamine is usually effective.

**Angioedema**

This is a variant of urticaria where massive edema involves subcutaneous tissues rather that the dermis. It may involve any part of the body surface like the lips, eyelids, tongue and larynx. This condition can be associated with urticaria of any cause. The hereditary form is caused by a quantative or functional deficiency of C1 esterase inhibitor and is inherited as an autosomal dominant trait. An acquired form of C1 esterase inhibitor may develop in patients with lymphoproliferative disorders and systemic lupus erythematosus.

**Hereditary Angioedema**

In hereditary angioedema attacks are infrequent in childhood, common in adolescence and early adult life and may subside later. It is precipitated by trauma and the lesions may affect the skin, mucosal surface and intestine. Subcutaneous swelling is not itchy and typically persisted for a few days. Intestinal edema may

cause symptoms simulating acute abdomen. Laryngeal edema may lead to upper airway obstruction and death. The C2 and C4 level are low in between attacks and C3 is normal. There is a low C1 esterase inhibitor level. In acute airway obstruction, subcutaneous adrenaline may be lifesaving. Fresh frozen plasma should be administered by intravenous infusion or, alternatively a purified C1 esterase inhibitor concentrate can be given. For long term management attenuated androgens stanozolol or danazol can be used for prophylaxis. They act by stimulating hepatic synthesis of C1 inhibitor. Antifibrinolytic agents like tranexamin acid and epsilon aminocaproic acid are less effective as prophylaxis but can be tried in patient who cannot tolerate androgenic steroids.

**Contact Urticarias**

Contact urticaria is a local immediate or delayed erythema or urticarial reaction at the site of epidermal or mucosal contact with a causative agent. It may be associated with generalized cutaneous reactions, rhinitis, asthma, or anaphylaxis. It is commonly an IgE mediated immediate reaction and non-immunological mechanism is also possible.

Probably the most important cause of contact urticaria is natural rubber latex present in gloves and other rubber products. Latex contact urticaria symptoms vary from mild itching to bronchial asthma, anaphylaxis, and death. Up to ten allergenic proteins have been isolated from latex. Small molecular weight chemicals may cause contact urticaria. Chemicals like ethylene oxide isocyanates, chloramines-T, epoxy resins and nickel sulphate can act as hapten and initiate IgE-mediated allergies. This can be confirmed by using skin prick testing.

**Urticariapigmentosa**

This condition is in fact not urticaria but is a disorder of mast cell proliferation commonly seen in early childhood. Clinically there are multiple guttate or larger pigmented macules on the trunk and limbs of the baby and urticated lesion may appear on rubbing the pigmented lesions. The biopsy of the skin shows increase in the number of mast cells.

## THERAPEUTIC MODALITIES FOR URTICARIA

**Antihistamines.** This group of drugs has H1 receptor blockers action and is the mainstay of therapy for urticarias. There are many antihistamines available. While the classical ones have been used for many years and are effective and cheap, they have more anticholinergic action and can cause more sedation. The newer antihistamines are more expensive and less sedating. In general there is little difference in the efficacy between the two groups of antihistamines and there are a lot of individual variations in response to treatment

As a guideline one should prescribe an antihistamine that one is familiar with and gradually titrate the dosage according to the response. It is worthwhile to switch to an antihistamine of another class if the response to the first choice is not

satisfactory when the maximum dosage has already been given. Alternatively, in order to select out the most suitable agent for the patient, an antihistamines self-assessment questionnaire can be employed.
The classical antihistamines (see Table 7.3) can be grouped into 6 classes according to their chemical structures, but the introduction of the newer drugs has greatly complicated this.

**Table7.3 Commonly Used "Classical" Antihistamines**

| Class | Generic name | Usual Adult Dose |
|---|---|---|
| Ethanolamines | Dimenhydrinate<br>Diphenhydramine | 50-100 mg qid<br>25-50 mg qid |
| Alkylamines | Chlorpheniramine<br>Dexrochlorpheniramine<br>Pheniramine | 4 mg tid<br>2-3 mg tid<br>75 mg bid |
| Phenidenes | Mebhydrolin | 50-100 mg tid |
| Phenothiazimes | Promethazine<br>Trimeprazine<br>Mequitazine | 10-25 mg bid<br>10-30 mg qid<br>5 mg bd |
| Piperazines | Hydroxzine | 10-25 mg tid |
| Piperidines | Cyproheptadine<br>Azatadine | 4 mg tid<br>1-2 mg tid |

Unwanted effects are common with these antihistamines, the commonest being sedation, dizziness, fatigue, insomnia and dry mouth. Paradoxical increase irritability may be seen in children. Alcohol can potentiate the sedative effect and patient should be advised to abstain from drinking while on antihistamine therapy. The anticholinergic action may cause urinary retention and precipitate glaucoma. All antihistamines are not proven safe in pregnancy and one should balance the risk and the possible benefit before prescribing antihistamines to pregnant woman. Newer antihistamines should always be avoided.

**Table7.4 Low SedatingAntihistamines**

| Usual adult dosage | Onset | Duration of action |
|---|---|---|
| Terfenadine 60 mg bd | 12-2 hours | > 12 hours *1 |
| Astemazole 10 mg daily | Days | 4 weeks *2 |
| Loratadine 10 mg daily | 1-2 hours | 24 hours |
| Cetirizine 10 mg daily | 1-2 hours | 24 hours |
| Acrivastine 8 mg tid | 30 minutes | 12 hours |
| **Notes**:<br>1. Fatal ventricular arrhythmia has been reported with larger than normal dose, in patients with liver disease and when it is administered with erythromycin or ketoconazole<br>2. Very long duration of action. Ventricular arrhythmia reported. Cautious in the elderly. Weight gain may occur during prolonged therapy. | | |

**Other antihistamines and related drugs**
Ketotifen: antihistamine-like drug with mast cell stabilizing effect, worth a try in difficult urticaria and when tolerance to antihistamine therapy appears. Adult dosage 1-2- mg bd.
Oxatamide: properties comparable to ketotifen, dosage is 30 mg bd.
Doxepin: tricyclic antidepressant with antihistamine activity. Suitable for administration at night. There is drug interaction with MAOIs, and can cause cardiac arrhythmia. Dosage: 10 mg nocte.

**H2-Receptor Blockers**
The exact mode of action of H2 antagonist in urticaria is still uncertain. In many stubborn cases addition of an H2 antagonist with an antihistamine may be helpful, but there is no ground to give an H2 antagonist alone. Cimetidine: 400 mg bd. Ranitidine: 150 mg bd.

**Beta-stimulants**
This is considered as a second line treatment for patients with resistant chronic urticaria and antihistamine tolerance. They act directly on the mast cell and prevent degranulation. Although they are effective, their use is limited by their side effects, including tremors and tachycardia. Salbutamol: 2-4 mg tid. Terbutalin: 0.5 mg tid.

**Calcium Channel Blocker**
Only nifedipine is useful for stubborn urticaria. It acts by stabilizing mast cell and inhibit degranulation. Side effects include hypotension and flushing attacks. Nifedipine: 5-10 mg tid.

**Anabolic steroid**
This has been used in patients suffering from hereditary angioedema. It is also used in cholinergic urticaria. Danazole: 100-600 mg daily. Stanozolol: 2-5 mg daily.

**Systemic corticosteroid therapy**
This is an effective form of therapy for urticaria but long term therapy should be used only in exceptional cases because of its side effects. Systemic steroid therapy is indicated for anaphylaxis and acute urticaria of serum sickness. For chronic urticaria, this should be avoided unless it is given for a short duration to tie over an acute episode.

**Mast Cell-Stabilizing Agents**
Disodium cromoglycate which stabilizes mast cell membrane has been found to be useful in atopic asthma when administered via an inhaler. Because the drug is not absorbed in the gastrointestinal tract they are generally not effective for patients with chronic urticaria. However, it may be helpful in cases of urticaria caused by food allergy. Two antihistamine, ketotifen and oxatamide, have additional mast

cell stabilizing effect but it is not certain whether this additional property is of any clinical significance.

**Immune Modulation**

Based on the autoimmune hypothesis for chronic idiopathic urticaria, various immune modulation therapies have been investigated for treatment of the condition: plasmapheresis, cyclosporine and intravenous immunoglobulin. These modalities are still experimental and not yet suitable for routine clinical application.

# VIII. PAPULOSQUAMOUS DISEASES

## 8.1 Psoriasis

**Introduction.** Psoriasis is one of the most common clinical dermatological conditions and recent evidence points to an etiology encompassing systemic, "immunologic", autoimmune and genetic elements. It is important to recognize that psoriasis is a term that embraces a spectrum of disease, ranging from localized plaques to more severe generalized involvement, with or without psoriatic arthritis and the associated manifestations of other autoimmune diseases. However, all patients, regardless of the severity of their condition, may suffer from a reduced quality of life, particularly in relation to work and social/personal interactions.

**Epidemiology.** Psoriasis is a common chronic inflammatory disease that affects approximately 2% of the population. Although all races are affected, there is considerable interracial variation. For example, psoriasis is relatively common in white people, but appears to be very uncommon in native American Indians and in Japanese people. Prevalence appears to be highest in Scandinavian countries and northern Europe. Men and women are affected equally. The usual age of onset is 20-35 years, with 75% of all cases occurring for the first time before the age of 40 years. However, psoriasis can occur at any age.

Based on the age of onset, human leukocyte antigen (HLA) association and disease course, two types of chronic plaque psoriasis have been described.

– Type I, the commonest form, occurs in young adults with a high probability of a positive family history. Affected individuals tend to have more severe disease that runs a more irregular course.

– Type II psoriasis has a peak incidence between 50 and 60 years of age. In these individuals, a positive family history is very uncommon and the disease tends to be mild and localized.

– Approximately 80% of patients with type I psoriasis are HLA-Cw6 positive, compared with only 20% of those with type II psoriasis.

Although psoriasis is rarely fatal, it severely affects a patient's quality of life, in terms of both psychological and physical well-being. Studies comparing psoriasis with other important chronic diseases have shown that the impact of psoriasis on the patient's quality of life is at least as great as that of ischemic heart disease, diabetes and chronic obstructive airways disease. Psoriasis is therefore a disease of major socioeconomic importance.

**Genetics**. The role of genetic predisposition in determining whether an individual develop psoriasis is at least as great as in many other chronic inflammatory diseases, including inflammatory bowel disease and multiple sclerosis. Many investigators are now using modern molecular genetics technology to try to unravel the genes that cause psoriasis. Such studies hold great promise for the development of highly specific treatments and new diagnostic and prognostic aids.

Numerous chromosomal loci have been discovered for psoriasis. However, only 30% of patients have a family history of the disease and it is not yet known how psoriasis is inherited. In some families, psoriasis appears to behave like an autosomal dominant disease, whereas in other cases there is little or no family history. It has been suggested that psoriasis may represent a spectrum of disease in which different genes, working either alone or in concert (polygenic disease), are important in different families.

**Environmental factors** also play a key etiologic role. For example, in 60% of patients with guttate psoriasis the disease was precipitated by systemic, usually upper respiratory tract, streptococcal infection. Other important environmental factors include drugs, particularly lithium and antimalarias, and physical or psychological stress. Excessive alcohol intake is also associated with disease deterioration and makes management more difficult.

**Pathopysiology.** Psoriasis is characterizes by bright red, elevated, scaly plaques. These clinical features mirror the characteristic pathophysiological events that occur in lesional skin.

***Epidermal hyperproliferation***. There is an increase in the number of proliferating keratinocytes in the basal layer of the epidermis. This, together with loss of differentiation, is responsible for the thick, silvery scale seen clinically. The growth rate of the psoriatic epidermis is up to 10 times that of normal epidermis.

***Expansion of the dermal vasculature.*** The blood vessels in the upper dermis become dilated and hyperpermeable, and actively increase in number. This expansion of the dermal vasculature accounts for the vivid red color of active plaques.

***Accumulation of inflammatory cells.*** These cells - neutrophils and T-lymphocytes in particular – accumulate in both the dermal and epidermal layers of the skin.

***Primary pathophysiological event.*** Most evidence indicates that lymphocytes play a key role in the disease process, and that the epidermal proliferation and loss of differentiation are secondary, a consequence of the release of mediators from infiltrating lymphocytes. Indeed, it has been postulated that psoriasis is an autoimmune disease. The observation of an increased prevalence of psoriasis among patients with other organ-specific inflammatory diseases, such as ulcerative colitis and Chrohn's disease is consistent with this hypothesis.

**Immunologic aspects**. Evidence that psoriasis is primarily an immunologic disease comes from many different sources. In evolving lesions, lymphocytes infiltrate early into the skin, prior to epidermal and other changes. Psoriasis is associated with certain HLA antigens, particularly HLA-Cw6 and HLA-B57, which are cell-surface molecules critical to the regulation of T-lymphocyte function.

Considerable progress has been made in identifying the precise lymphocytes that cause the disease. However, the antigens- foreign or auto – to which these lymphocytes are responding are currently unknown.

## Box 8.1 Key Points – Epidemiology and Pathophysiology

- Psoriasis affects approximately 2% of the population; however, there is considerable interracial variation in prevalence.
- The usual age of onset is 20 – 35 years.
- There is a family history of psoriasis ion 30% of patients.
- There is growing evidence that psoriasis is primarily an immunologic T-cell-driven disease.
- Important environmental triggers include infection, drugs, and physical and psychological stress.
- Three key events characterize the pathophysiology of psoriasis: epidermal hyperproliferation, angiogenesis and accumulation of inflammatory cells.
- The impact of psoriasis on the patient's quality of life is similar – physically and emotionally – to that of ischemic heartdisease, diabetes or chronic obstructive airways disease.

## Clinical Presentation

Chronic plaque psoriasis (psoriasis vulgaris) accounts for approximately 85% of all cases of psoriasis. The majority of patients develop clinical signs of psoriasis before the age of 35 years, with about 10% of patients developing the condition during childhood. A history of long-standing "dandruff" scaling in the ears, pruritus ani or vulvae, arthralgias or the presence of other autoimmune disease, such as inflammatory bowel disease, diabetes or thyroid disease, may be clues to a diagnosis of psoriasis. There is no blood test specific to psoriasis

## Table 8.1 Important Factors in Patient's History

| |
|---|
| **Medical history**<br>• Persistent scaling in the ears<br>• Concomitant or previously diagnosed autoimmune disease<br>• Joint problems<br>• Long-standing "dandruff"<br>• Pruritus ani or vulvae |
| **Family history**<br>• Psoriasis<br>• Rheumatoid disease |
| **Precipitating factors**<br>• Antecendent infections (particularly streptococcal)<br>• Physical trauma<br>• Emotional or metabolic stress |
| **Drugs likely to exacerbate psoriasis**<br>• Antimalarials (e.g. chloriquine)<br>• Interferons<br>• Lithium<br>• Systemic glucocorticoids |
| **Clinical manifestations**<br>Psoriasis exhibits a range of histological features. All lesions show varying |

degrees of three cardinal characteristics:
- Scaling
- Thickening (induration)
- Inflammation (redness).

## Box 8.2 Histological Features of Psoriasis

- ✓ **Parakeratosis:** retention of nuclei in the stratum corneum
- ✓ **Suprapapillary thinning**: only a few layers of epidermal cells are observed above the dermal papillae
- ✓ **Papillary elongation**: increased lengthening of the papillary folds
- ✓ Increased prominence of the **papillary acantosis**: thickening of the epidermis vasculature
- ✓ **Squirting papillae**: neutrophils noted in the dermal papillae and frequency in the adjacent epidermis. This may even produce microabscesses in the more inflammatory or pustular variants
- ✓ Chronic **perivascular inflammatory response** noted in the dermis

The classic symmetry, silvery scale and vivid reddish-purple color allow psoriasis to be easily differentiated from other skin disorders in the majority of cases.

**Shape of lesions.** Classically, a psoriatic lesion is oval-shaped (discoid), although atypical lesions featuring linear, annular or geographic "map-like" configurations may be present. Other morphological variants, which can coexist in one patient, include:
- Guttate lesions (predominantly on the trunk)
- Flexural forms (body folds)
- Erythrodermic psoriasis (total body erythema and scaling)
- Pustular psoriasis (localized or generalized)
- Localized variants, such as palmar-plantar forms.

***Guttate lesions*****,** approximately 1 cm in diameter, often follow a streptococcal infection in younger patients. Multiple "drop-like" lesions occur and are typically distributed on the trunk; they may develop rapidly over a period of a week. Larger plaques may be seen in areas such as the lumbar-sacral region, and frequently involve the natal cleft with extensionto perianal areas.

***Flexural forms***(inverse psoriasis), commonly seen in obese patients, occur in normal body folds, such as under the breasts, and in the inguinal and axillary regions.

***Erythrodermic psoriasis***is relatively uncommon. It involves the entire body surface and may be precipitated by inappropriate use of systemic glucocorticoids, infections or even phototherapy or sunburn. Patients are febrile, and often have high white-cell counts and problems with temperature control. Associated ankle edema is common. Frequently cardiac and renal decompensation is seen, particularly in the elderly.

***Pustular psoriasis***can appear as two forms. The first form occurs in association with erythrodermic psoriasis, in which multiple tiny pustules. With or without coalescence, are scattered throughout the inflamed body surface. The second is a more localized form in which multiple small pustules, often on an erythematous and hyperkeratotic base, are present on the palms and soles; this is sometimes referred to as palmar-plantar pustulosis.

**Distribution** of psoriatic lesions is highly symmetrical in most cases, except when modified, for example, by chronic scratching on the back or sides of the scalp. Regions commonly involved include the thicker areas of the skin, such as the scalp, elbows, knees, sacral area and knuckles on the hand dorsa. Although psoriasis is normally considered to be a non-itchy condition, the majority of patients quickly develop the habit of scratching, leading to a marked increase in thickening (lichenification) of individual plaques. Similarly, day-to day trauma may modify lesions in areas such as the hands and feet.

Secondarily candidiasis in body folds can also modify psoriasis, as can concurrent disease such as human immunodeficiency virus (HIV) infection, which frequently results in a more inflammatory form of psoriasis, often with severe facial involvement.

**Color of lesions.** Psoriasis lesions are usually a more vivid purplish-red color than most other dermatoses, such as eczema. Even in early lesions, gentle scratching of the affected skin will elicit the classic silvery scale. Gentle detachment of the overlying silvery scale will produce fine, pinpoint bleeding on the surface of the skin; this is known as the Auspitz sign and is highly diagnostic.

**Sites of disease involvement.** For diagnosis, the whole body surface should be evaluated. Similarly, the total skin area should be assessed when deciding on appropriate treatment.

***Scalp***involvement may range from a moderate degree of silvery scale, resembling seborrheic dermatitis, to thick well-circumscribed plaques, covering major portions of the scalp surface. The patient's habitual scratching will often modify the psoriasis to produce asymmetric plaques, particularly on the sited and the posterior scalp. Extension beyond the scalp fringes onto the forehead, temples, sideburns and nape of the neck is common.

***Ears*.** The retroauricular folds, which extend into the scalp margin, are a common site of involvement, often producing secondary fissuring. Psoriasis is also one of the most common causes of otitis externa, with a classic silvery scale on an erythematous base extending into the ear canal. Wafting of the scale down the ear canal may produce a pseudo-membrane, which may impair hearing with time.

***Face*.** Involvement of the face is not uncommon. Scaling, erythema and even plaque formation may be noted in the eyebrows, together with scaly erythema around the sides of the nose, scalp and sideburn fringes, which extend onto the forehead and temple regions. In addition, men frequently develop psoriasis within the beard region, particularly the sides of the neck, because of shaving trauma.

***Trunk*.** Individual discoid plaques are usually seen in this region. There is great variation in size and shape, but larger plaques are often noted in the lumbar-sacral

area. Involvement of the umbilicus and gluteal cleft is common. Lesions in the folds of the breasts are also common – usually the classic silvery scale is not seen, but a distinct erythema is present. In the flexures, secondary candidiasis, with development of pustules peripheral to the well demarcated erythematous areas, is a common sequels.

***Extremities.*** Localized discoid plaques are common on the elbows and knees. Symmetrical discoid plaques, ranging in size and number are particularly prominent on the distal portions of the extremities, particularly the shins and ulnar surface of the arms.

***Hands and feet.*** Two main forms of psoriasis occur at these sites

- The hyperkeratotic variant has localized well-circumscribed or more diffuse erythematous silvery plaques, with or without fissures. There is frequent involvement of the palmar surface and sides of the fingers
- The pustular variant has multiple tiny pustules (0.1-0.3 cm in diameter), with or without associated erythema, scaling or crusting of the intervening skin. These pustules are sterile and are caused by accumulation of polymorphonuclear leukocytes within the epidermis.

***Genitalia*** are frequently involved. In men, a well-circumscribed, thin, erythematous lesion is seen on the glans penis, usually with minimal associated silvery scale because of the thinness of the skin in this region. In women, a similar, well-circumscribed, purplish-red erythema is noted enveloping the vaginal opening. The pubic region is often involved in both sexes. Direct extension of disease from the natal cleft may involve perianal skin and cause pruritus ani.

***Nails.*** Involvement of the nails can take several forms.

*Pitting* describes discrete, well-circumscribed depressions of about 1 mm in diameter on the nail surface. This may involve only a few nails or the majority of the fingernails and to a lesser degree, the toenails.

*Onycholysis* is a separation of the nail from the nail bed at its free edge. It produces a white to yellowish discoloration of the distal nail plate, ranging from 1-2 mm at the distal free edge to involvement of the entire nail.

*Subungual hyperkeratosis***.** Silvery white crusting and debris are seen underneath the free edge of the nail in association with some degree of thickening of the nail plate.

**"***Oil-drop sign***"** refers to the well-circumscribed, usually circular, light pink-to-red color change seen on the surface of the nail, separate and distinct from onycholysis.

**Koebner phenomenon,** also known as isomorphic response, describes induction of psoriasis as a result of trauma at sites of previous non-involvement. It occurs at scratches, surgical incisions, body-piercing sites and scars, and with friction from clothing or jewelry, such as rings, watches and earrings.

**Psoriatic joint disease**. On clinical and radiological evaluation, approximately 25% of patients have confirmed psoriatic arthritis. Many more complain of mild

arthralgias. Five major pattern of psoriatic arthritis are recognized, with overlapping clinical expressions frequently seen:

- Distal interphalangeal involvement
- Symmetrical polyarthritis, indistinguishable from rheumatoid arthritis
- Asymmetrical oligoarthritis
- Psoriatic spondylarthropathy
- Arthritis mutilans, a rare variant that is most likely to affect the hands and feet
- Patients with the most common form – distal interphalangeal disease – frequently have concomitant nail disease, often localized to the same digits as the joint disease.

**Box 8.3 Key Points – Clinical Presentation**

- Medical history, family history and physical examination are all important in establishing the diagnosis of psoriasis
- Psoriasis is a clinical diagnosis; there is no blood tests specific for this disease
- Chronic discoid plaque psoriasis is the most common subtype of psoriasis
- The scalp, elbows, knees and sacrum are the areas most commonly affected by psoriasis
- Psoriasis can sometimes be triggered by infection, trauma, stress or medications

## DISEASE MANAGEMENT

The overall goals of any treatment program for psoriasis must be to:

- improve the patient's quality of life
- achieve long-term remission and disease control
- reduce individual drug toxicity
- carefully evaluate individual treatments and monitor their cost-effectiveness

### Available Treatments

Treatments available for psoriasis include a wide range of topical therapies, phototherapy (including photochemotherapy) and a variety of systemic agents, some with potentially significant side effects (see Table 4). Many factors influence the choice of therapy for an individual (see Table 5). Approximately 70% of patients with psoriasis can be managed using topical therapy alone.

## Table 8.2 Conventional Psoriasis Therapies

| Level 1<br><br>Topical therapies | Level 2<br><br>Photo therapies | Level 3<br><br>Systemics (high efficacy, high toxicity) | Level 4<br><br>Systemics (moderate efficacy, moderate toxicity) | Level 5<br><br>Systemic therapies (moderate efficacy, high toxicity |
|---|---|---|---|---|
| Emollients<br>Keratolytics<br>Dithranol<br>Vitamin D3 analogs (calcipotrien)<br>Corticosteroids<br>Coal tar<br>Topical retinoids (Tazarotene) | Sunlight<br><br>UVB<br><br>UVB+ coal tar<br><br>UVB+anthralin<br><br>UVB narrowband | Psoralen+UVA<br><br>Psoralen+UVA +UVB<br><br>Acitretin<br><br>Methotrexate<br><br>Cyclosporine | Sulfasalazine<br><br>Hydroxyurea<br><br>Calcitrol<br><br>Antibiotics | Azathioprin<br><br>6-thioguanine<br><br>Tacrolimus |

## Box 8.4 Factors to Consider When Treating Psoriatic Patients

- Patient's perception of disease severity
- Objective measures of the pattern, extent and severity of disease
- Amount of time the patient is able to devote to therapy
- Previous treatments for psoriasis
- Coexistent medical problems
- Other drug therapy

Before beginning therapy, the patient should have a realistic expectation of the outcome. In practice, this means explaining that treatment will be lengthy and is not curative, and that the psoriasis is likely to relapse if therapy is discontinued. In addition, it is crucial to spend sufficient time explaining practical aspects, such as:

- Precisely what a treatment is designed to achieve and how
- Where and for how long therapy should be applied
- Any local side effects, such as irritation, staining or smell.

### Topicaltreatments

Topical therapy remains the mainstay in the management of psoriasis as the majority if patients achieve adequate control of their lesions with topical agents. Besides, topagents are prescribed as a rule in patients who are treated with systemic agents.

**Table 8.3 Topical Therapies for Chronic Plaque Psoriasis**

| Agent | Efficacy | Relapse rate | Side effects | Cosmetic problems |
|---|---|---|---|---|
| Emollients | + | + | - | + |
| Keratolytics | + | + | + | + |
| Coal tar | ++ | + | + | ++ |
| Dithranol | +++ | + | + | ++ |
| Corticosteroids (potent/very potent) | +++ | ++ | ++ | - |
| Vitamin D3 analogs(Calcipotriol) | +++ | + | + | - |
| Topical retinoids (Tazarotene) | ++ | + | ++ | + |

- little or none
+++ very great or frequent (or in case of side effects and cosmetic problems, severe)

***Emolients.*** According to the classic textbook description psoriasis does not itch. However, a recent survey suggests that itching is a prominent and troublesome symptom in more than 60% of patients with psoriasis. Regular use of an emollient, particularly in colder months can alleviate pruritus, reduce scale and enhance penetration of concomitant topical therapy.

***Keratolytic agents.*** Agents such as salicylic acid and urea are often included in topical psoriasis preparations, especially in case of prominent hyperkeratosis; they reduce scale and enhance penetration id other active agents. Both salicylic acid in concentrations of 10% on an ointment or propylene glycol 50% in water under plastic occlusion are effective keratolytic approaches.

***Coal tar***. Crude coal tar is effective in the treatment of psoriasis. Especially in itchy, unstable psoriasis, tar treatment can be very effective with a pronounced antipruritic effect. In patients with pustular psoriasis and erythrodermic psoriasis, the concentration of coal tar should be low to avoid irritation. In view of the staining by tar, this treatment only is successful if careful instruction is guaranteed. Coal tar should be avoided during pregnancy and lactation.

***Dithranol*** (anthralin). Dithranol has been used in the treatment of psoriasis for more than 80 years. It includes a cascade of free radicals, which is reputed to be the antipsoriatic action. Dithranol is indicated in patients with chronic plaque psoriasis and in general for those patients whose psoriasis cannot be controlled by vitamin $D_3$ and corticosteroid treatments. Dithranol is contraindicated in patients with pustular erythrodermic and unstable relapsing psoriasis as patients with these conditions may respond with severe irritation which can be problematic to manage. The clinical efficacy of dithranol approaches that of major treatments such as PUVA and systemic treatments provided that treatment is performed adequately at an in-patient department. Prescription as a cream for short contact treatment and application by the patients at home is less effective. Side effects are the staining of skin, which reaches a maximum 48-73 hours after application. In view of side effects but also in view of the need for concentration adjustment up to “minimal

irritancy", dithranol treatment is only effective if the patient is treated at an experienced unit under intense supervision.

***Corticosteroids.*** Since 1963, topical corticosteroids have been an important treatment modality for psoriasis. Topical corticosteroids are indicated if fast induction of a remission is required. In the case of dermatitis perioralis or atrophic changes of the skin due to overtreatment with topical corticosteroids, topical steroid treatment is contraindicated.

The clearing capacity of potent topical corticosteroids is excellent, especially if these compounds are prescribed to a patient for the first time. The efficacy of topical corticosteroids is enhanced considerably by using occlusion; hydrocolloid occlusives are especially well tolerated. The value of topical corticosteroids as a maintenance therapy is less convincing as a hazard of long-term corticosteroid treatment is atrophy of the skin, resulting in striae, teleangiectasias and purpura. Other side effects include hypertrichosis, perioral dermatitis and allergic contact dermatitis. Potent topical corticosteroids may also suppress plasma cortisol levels.

In general, patients should be treated once daily, although intermittent treatment (once/twice weekly) has been claimed to be very effective. The application of topical corticosteroids over large areas of the skin should be avoided.

***Vitamin $D_3$ analogues.*** In 1992 **calcipotriol** was introduced as a treatment for psoriasis. In view of the excellent therapeutic efficacy and the limited toxicity, calcipotriol has become a frequently used treatment in chronic plaque psoriasis.

Calcipotriol is now the first line treatment for patients with chronic plaque psoriasis. Comparative studies between calcipotriol and other treatment revealed that calcipotriol is at least as effective as betamethasone or dithranol outpatient treatment. Irritation of the skin is observed in up to 20% of patients, requiring discontinuation in only 5% of these. If no bone or kidney disease exists, hypercalcaemia will not be observed at weekly doses of less than 100 g calcipotriol cream or ointment.

Calcipotriol cream or ointment is a first line treatment for psoriasis. As a rule twice daily application is advised as the most effective dose schedule. Not more than 100 g of ointment per week should be used. Calcipotriol should not be applied in the face and body folds. Children and patients with kidney disorders are more at risk of developing hypercalcaemia during treatment with calcipotriol.

***Topical retinoids (tazarotene).*** Tazaroten is the first retinoid which proved to have an antipsoriatic effect following topical application. In concentrations up to 0.1% in gel formulation, the compound was effective and showed an acceptable tolerability in the treatment of chronic plaque psoriasis. In a comparative study, once daily treatment with Tazaroten 0.1% gel approached the efficacy of fluocinonide cream with respect to induration and scaling. However fluocinonide induced a more substantial reduction of erythema as compared to Tazarotene.

**Box 8.5Key Points – Topical Therapy**

- Approximately 70% of patients (those with mild or moderate disease) can be managed using topical therapy alone.
- Time spent detailing the practicalities of topical therapy is crucial to achieving a successful therapeutic outcome.
- A wide variety of topical therapies is available; topical corticosteroids and vitamin $D_3$ analogs are considered first-line therapy for most patients.
- Efficacy and cosmetic acceptability are key determinants of patient concordance with therapy.
- Consideration should be given to the body site being treated, since this influences which active ingredient and formulation should be prescribed.

## Photo(chemo)therapy

Ultraviolet radiation has an important therapeutic effect in psoriasis. Ultraviolet B (UVB) radiation (290-320nm) has a substantial photodynamic effect, as the radiation penetrates into the dermal-epidermal transition zone. The therapeutic efficacy of UVB phototherapy in psoriasis is satisfactory in the majority of patients. By contrast, the therapeutic effect of UVA (320-400nm) is limited. Although the radiation penetrates into the deeper layers of the skin, the quantum energy of UVA radiation it too low for a substantial anti-psoriatic effect. With the combination of ultraviolet A and the ingestion or topical application of a psoralen, a substantial photodynamic and anti-psoriatic effect can be achieved. Both phototherapy with UVB and photochemotherapy require dose management to minimize irritation of the skin.

Phototherapy with UVB is indicated in extensive chronic plaque psoriasis and guttate psoriasis. In generalized pustular psoriasis and erythrodermic psoriasis, restricted use or caution with respect to phototherapy is advised.

Although several studies have demonstrated the carcinogenic potential of phototherapy in humans, the risk of inducing cancer of the skin with UVB treatment is minimal. Contraindications for phototherapy are photodermatoses, the ingestion of phototoxic medication, a previous history of skin cancer and actinic keratosis as well as previous treatment with X-rays, or arsenic ingestion. A family history of melanoma is also regarded as a contraindication for phototherapy.

Photochemotherapy (PUVA) has a substantially increased anti-psoriatic potential compared to phototherapy with UVB. Side effects of photochemotherapy are erythema, bullae, burning, nausea, itching, and pigmentations. PUVA-lentigines, hypertrichosis and pain. Following long-term treatment with PUVA, multiple squamous cell carcinomas have been induced. Contraindications for PUVA are the same as for UVB, although the side effects of PUVA are more severe compared with UVB. Chronic side effects of PUVA are cataract and hepatotoxicity.

PUVA treatment is indicated in extensive psoriasis, including generalized pustular psoriasis, pustulosis palmoplantaris and erythrodermic psoriasis. In the Scandinavian countries, bath-PUVA has already been applied for some years. The

psoralen is applied via a bath and patients are subsequently treated with UVA. The advantage of bath-PUVA is the reduced occurrence of nausea. The long-term risk with respect to the induction of squamous cell carcinomata has been reported to be reduced with bath-PUVA compared to systemic PUVA treatment. It is of practical relevance that patients using systemic medication with a phototoxic potential should refrain from photochemotherapy or alternatively should discontinue the phototoxic medication. Patients using immunosuppressive treatment should refrain from photochemotherapy as this combination can have a carcinogenic effect. Recently, it was demonstrated that patients receiving 250 PUVA treatments or more has an increased risk of malignant melanoma. Therefore, the cumulative carcinogenic risk of PUVA treatment should not be underestimated.

**Box 8.6 Key Points – Phototherapyandphotochemotherapy**

- Phototherapy (broad-band UVB and narrow-band UVB) is widely used for extensive chronic plaque psoriasis and sebo-psoriasis, and persistent guttate psoriasis.
- Burnig and, rarely, photosensitive rashes complicate phototherapy in the short term.
- There is a small increase in the risk of non-melanoma skin cancer with long-tern phototherapy.
- Photochemotherapy (PUVA) is indicated for patients with moderate-to severe psoriasis involving more than 10% of the body surface area, and those whose psoriasis does not respond to topical therapy.

- Short-term risks of PUVA include nausea (following oral ingestion of psoralen), itching and phototoxic reactions.
- Long-term risks of PUVA include premature skin aging and skin cancer (non-melanoma and melanoma).
- In patients who already have risk factors for skin cancer, phototherapy and photochemotherapy should be prescribed only with extreme caution.

## Systemictherapy

In case of recalcitrant manifestations of chronic plaque psoriasis, erythrodermicpsoriasis and generalized pustular psoriasis, a systemic treatment may be indicated. Methotrexate, acitretin and cyclosporine are the well-established treatments for psoriasis.

***Methotrexat*e** is very effective in nearly all forms of psoriasis. Intermittent treatment is indicated in order to reduce the toxic potential of this drug. In general, the treatment is prescribed according to the following scheme: three ingestions at 12-h intervals per week. A maximum dose of 15 mg methotrexate per week is advisable. According to the literature, however, doses between 22.5 and 30 mg are acceptable. Side effects include anorexia, nausea, alopecia, leukopenia, thrombocytopenia, megaloblastic anemia. Methotrexate may induce fibrosis and cirrhosis of the liver. In women and men who wish to have children in the short-tern, the mutagenic effect of methotrexate has to be considered. Male and female patients must use continuous contraception for at least 6 months after discontinuing methotrexate treatment. Contraindications for methotrexate

treatment are substantial lever and kidney diseases, pregnancy, a desire to procreate in the short-term, active infections, interaction with other medication, bone marrow hypoplasia, peptic ulceration, ulcerative colitis and patient non-cooperation. During treatment, patients are advised not to take alcohol during the days of methotrexate ingestion. Patients should be at the out-patients department at 4- to 6-week intervals. Before treatment and after the cumulative dose of 1.5 mg methotrexate, a liver biopsy is indicated in order to assess the histological appearance of the liver.

***Acitretin*** is a retinoic acid derivative which is indicated as a monotherapy in erythrodermic and pustular psoriasis. In the case of chronic plaque psoriasis, this treatment is very effective in combination with phototherapy (UVB) or photochemotherapy (PUVA). The dose of acitretin varies between 25 and 75 mg/day. Side effects include dry lips, epistaxis, conjunctivitis, pruritus, skin atrophy, alopecia,and dermatitis, decreased visual perception at night, color blindness and hyperlipidemia. Incidentally, hepatitis and increased osteophyte formation have been recorded. Women, wishing to become pregnant, must not take acitretin due to its teratogenic potential. Pregnancy should be excluded before initiation of acitretin treatment and for a period of at least 2 years following discontinuation of treatment. No restrictions with respect to male patients should be given. Contraindications for treatment with acitretin are liver disease, hyperlipidemia, pregnancy and the desire to become pregnant. Before treatment and at monthly intervals, patients should be seen at the out-patient department, and serum triglycerides, serum cholesterol and liver function tests mist be carried out. Before treatment and at yearly intervals, X-ray examination of the spine is advised. Active questioning of the patients with respect to joint complaints is indicated.

***Cyclosporin*** is effective in nearly all forms of psoriasis. The dose is between 3 and 5 mg/kg/day. Side effects are nephrotoxicity, hypertension, gingival hyperplasia, tremors, hypertrichoses, headache, diarrhea, general feeling of discomfort and nausea. Contraindications are nephrotoxicity, cytotoxicity, and immunosuppressive co-medication, X-ray exposure, concurrent photo (chemo) therapy, malignancies, active infections, immunodeficiency, organ defects, drug abuse, epilepsy, pregnancy, kidney dysfunctions and unmanageable hypertension. The patient should be seen once every 4-6 weeks. Kidney functions, blood pressure, liver functions and hematological investigations must be carried out during each visit.

***Biological response modifiers.*** Biological response modifiers are likely to revolutionize the treatment of moderate–to-severe psoriasis. They include agents that target T-cells and inflammatory cytokines. Biologic agents appear to alleviate the skin symptoms of psoriasis, improve patient quality of life, and in some cases arrest the progression of joint damage that disables some psoriasis patients. Biological modifiers have the advantage over traditional therapies of no apparent organ toxicity, including renal toxicity and hepatotoxicity. Individual drugs may prove to induce sustained, drug-free remissions in patients with psoriasis.

## Table 8.4Characteristics of BIological Response Modifiers

| Name | Dose regimen | Selected side effects | Stage of developments |
|---|---|---|---|
| **Alefacept** | 7,5 mg i.v. or 15 mg i.m. every week for 12 weeks | CD4 suppression; must monitor CD4 weekly | Moderate-to severe psoriasis |
| **Efalizumab** | 1 mg/kg s.c. every week | Headache, nausea, chills | Moderate-to severe psoriasis |
| **Etanercept** | 50 mg s.c. twice a week for 12 weeks, then 25 mg twice a week | Injection site reactions; multiple-sclerosis-like syndrome | Moderate-to severe psoriasis, psoriatic arthritis, rheumatoid arthritis; ankylosing spondylitis |
| **Infiximab** | 5 mg/kg i.v. infusion at 0.2 and 6 weeks; then every 8 weeks | Infusion reactions, reactivation of tuberculosis | Chrohn's disease, rheumatoid arthritis Moderate-to severe psoriasis, psoriatic arthritis |

Studies are underway to determine the optimal ways of combining biological agents with traditional therapies such as phototherapy, retinoids, methotrexate and topical medication.

### Box 8.7 Key Points – Biological Response Modifiers

- Biological response modifiers ("biologics") are a new class of drugs, widely available for several years, they target specific molecules involved in the immunopathogenesis of immune-mediated diseases such as psoriasis, psoriatic arthritis, rheumatoid arthritis and Crohn's disease.
- The biologics currently available or in clinical trials are all given by injection (subcutaneous, intramuscular or intravenous).
- Evidence to date suggests that biologics do not have toxic effects on internal organs.
- Some of these agents may offer long-term remissions for patients with psoriasis.
- Cost and long-tern safety will be important in determining the future role of biologics in the treatment of psoriasis.

## Combinationtherapy

Combination treatment is frequently used in the day to day management of psoriasis. Some combinations may have an additive clinical effect. Some combinations are useful in reducing the side effects. Table 7 provides an overview of recommended and contraindicated combinations.

**Table 8.5 Combinations in treating psoriasis**

| Therapies | Topical Vitamin D | Topical Cortico-steroids | Dithranol | Coal tar | UV B | PUVA | Metho-trexate | Cyclo-sporin |
|---|---|---|---|---|---|---|---|---|
| Acitretin | ++ | + | + | + | ++ | ++ | - | - |
| Cyclosporin | ++ | + | + | + | - | - | - | |
| Methotrexate | + | + | + | + | - | - | | |
| PUVA | ++ | + | + | + | - | | | |
| UVB | +/++ | + | +/++ | +/++ | | | | |
| Coal Tar | + | + | +/++ | +/++ | | | | |
| Dithranol | + | + | | | | | | |
| Topical corticosteroids | +/++ | | | | | | | |
| - + = recommended combination<br>- = contraindicated combination<br>- ++ = strongly recommended combination | | | | | | | | |

## 8.2. Lichen Planus

**Background:** Lichen planus (LP) is a pruritic, papular eruption characterized by its violaceous color; polygonal shape; and, sometimes, fine scale. It is most commonly found on the flexor surfaces of the upper extremities, on the genitalia, and on the mucous membranes. LP is most likely an immunologically mediated reaction.

**Pathophysiology:** LP is a cell-mediated immune response of unknown origin. LP may be found with other diseases of altered immunity; these conditions include ulcerative colitis, alopecia areata, vitiligo, dermatomyositis, morphea, lichen sclerosis, and myasthenia gravis. An association is noted between LP and hepatitis C virus infection, chronic active hepatitis, and primary biliary cirrhosis.

**Causes:** The exact cause of LP is not known. The pathogenesis of LP is immunologically mediated. Whether the foreign antigen is a virus or a drug is not known. Langerhans cells process antigens, which are then presented to T lymphocytes. This stimulated lymphocytic infiltrate is epidermotropic and attacks keratinocytes. During this lymphocytotoxic process, the keratinocytes release cytokines that attract more lymphocytes. This process has been referred to as the lichenoid tissue reaction. Also, recent studies reveal a disruption in the epithelial anchoring system.

Some patients with LP have a positive family history. It has been noted that affected families have an increased frequency of human leukocyte antigen B7 (HLA-B7). Others have found an association between idiopathic LP and human leukocyte antigen DR1 (HLA-DR1) and human leukocyte antigen DR10 (HLA-DR10); thus, LP may be influenced by a genetic predisposition.

**Mortality/Morbidity:** Cutaneous LP does not have a higher risk of skin cancer, but ulcerative lesions in the mouth, particularly in men, have a higher incidence of malignant transformation. Vulvar lesions in women may also be associated with squamous cell carcinoma.

**History:** Most cases are insidious. The initial lesion is usually located on the flexor surface of the limbs, such as the wrists. After a week or more, a generalized eruption develops with maximal spreading within 2-16 weeks.Pruritus is common but varies in severity depending on the type of lesion and the extent of involvement. Hypertrophic lesions are extremely pruritic.Oral lesions may be asymptomatic or have a burning sensation, or they may even be painful if erosions are present.In more than 50% of patients with cutaneous disease, the lesions resolve within 6 months, and 85% of cases subside within 18 months. On the other hand, oral LP had been reported to have a mean duration of 5 years. Large, annular, hypertrophic lesions and mucous membrane involvement are more likely to become chronic.

**Physical:** In addition to the cutaneous eruption, LP can involve the mucous membranes, the genitalia, the nails, and the scalp. The clinical presentation of LP has several forms: actinic, annular, atrophic, erosive, follicular, guttate, hypertrophic, linear, and vesicular. The papules are violaceous, shiny, and polygonal; varying in size from 1 mm to greater than 1 cm in diameter. They can be discrete or arranged in groups of lines or circles. Characteristic fine, white lines, called Wickham stria, are often found on the papules.

- Mucous membrane involvement is common and may be found without skin involvement. Lesions are most commonly found on the tongue and the buccal mucosa; they are characterized by white or gray streaks forming a linear or reticular pattern on a violaceous background. Oral lesions are classified as reticular, plaque-like, atrophic, papular, erosive, and bullous. Ulcerated oral lesions may have a higher incidence of malignant transformation in men, but this observation may be confounded by other factors, such as smoking and chewing tobacco. Lesions may also be found on the conjunctivae, the larynx, the tonsils, the bladder, the vulva, and the vaginal vault; throughout the gastrointestinal tract; and around the anus.
- Genital involvement is common in men with cutaneous disease. Typically, an annular configuration of papules is seen on the glans. Less commonly, linear white striae, similar to the lesions on the vulva and the vagina, can be seen on male genitalia. Vulvar involvement can range from reticulate papules to severe erosions. Dyspareunia, a burning sensation, and pruritus are common. Vulvar and urethral stenosis can also be present.
- In 10% of patients, ungual findings are present. Most commonly, nail plate thinning causes longitudinal grooving and ridging. Hyperpigmentation, subungual hyperkeratosis, onycholysis, and longitudinal melanonychia can result from LP. Rarely, the matrix can be permanently destroyed with prominent pterygium formation. LP has been linked to childhood idiopathic nail atrophy and may overlap with twenty-nail dystrophy of childhood.

• Patients with a cutaneous eruption may also have follicular and perifollicular violaceous, scaly, pruritic papules on the scalp. These lesions can progress to atrophic cicatricial alopecia that can appear many weeks after the skin lesions have disappeared. Pseudopelade can be a final endpoint.

• Variations in LP include the following:

***Hypertrophic***: These extremely pruritic lesions are most often found on the extensor surfaces of the lower extremities, especially around the ankles. Hypertrophic lesions are often chronic; residual pigmentation and scarring can occur when the lesions eventually clear.

***Atrophic***: Atrophic LP is characterized by a few lesions, which are often the resolution of annular or hypertrophic lesions.

***Erosive***: These lesions are found on the mucosal surfaces and evolve from sites of previous LP involvement.

***Follicular***: Lichen planopilaris is characterized by keratotic papules that may coalesce into plaques. This condition is more common in women than in men, and ungual and erosive mucosal involvement is more likely to be present. A scarring alopecia may result.

***Annular***: LP papules that are purely annular are rare. Annular lesions with an atrophic center can be found on the buccal mucosa and the male genitalia.

***Linear***: Isolated linear lesions may form a zosteriform lesion, or they may develop as a Koebner effect.

***Vesicular and bullous***: Most commonly, these lesions develop on the lower limbs or in the mouth from preexisting LP lesions. A rare condition, lichen planus pemphigoides, is a combination of both LP and bullous pemphigoid.

***Guttate***: These discrete lesions can range from 1 mm to 1 cm in diameter. They almost never become chronic.

***Actinic***: Subtropic or actinic LP occurs in regions, such as Africa, the Middle East, and India. This mildly pruritic eruption usually spares the nails, the scalp, the mucous membranes, and covered areas. Lesions are characterized by nummular patches with a hypopigmented zone surrounding a hyperpigmented center.

**Complications.**Oral ulcerations have the potential to become malignant. Malignant transformation has been reported in ulcerative oral lesions in men.Infection, osteoporosis, adrenal insufficiency, bone marrow suppression, renal damage, hyperlipidemia, and growth retardation in children may occur due to medication. Alopecia is often permanent. Hypertrophic lesions may leave residual hyperpigmentation. Vulvar lesions can be pruritic and painful.

**Lab Studies.**Direct immunofluorescence study reveals globular deposits of immunoglobulin M (IgM) and complement mixed with apoptotic keratinocytes.

**Histologic Findings.**The histopathologic features distinguish LP based on the presence of irregular acanthosis and colloid bodies in the epidermis with liquefactive degeneration and linear fibrin deposition in the basal layer. The upper dermis has a band-like infiltrate of lymphocytes and histiocytes. The inflammatory reaction pattern is characteristic. The epidermis is hyperkeratotic with irregular acanthosis and focal thickening in the granular layer. Degenerative keratinocytes,

known as colloid or Civatte bodies, are found in the lower epidermis. In addition to apoptotic keratinocytes, colloid bodies are composed of globular deposits of IgM (occasionally immunoglobulin G [IgG] or immunoglobulin A [IgA]) and complement. Linear or shaggy deposits of fibrin and fibrinogen and liquefaction are in the basement membrane zone.

The upper dermis has a band-like infiltrate of lymphocytic (primarily helper T) and histiocytic cells with many Langerhans cells. The infiltrate is very close to the epidermis and often disrupts the dermal-epidermal junction.

**Medical Care.**LP is a self-limited disease that usually resolves within 8-12 months. Mild cases can be treated symptomatically with antihistamines and fluorinated topical steroids. More severe cases, especially those with scalp, nail, and mucous membrane involvement, may need more intensive therapy.

The first-line treatments of cutaneous LP are topical steroids, particularly class I or II ointments. A second choice would be systemic steroids for symptom control and possibly more rapid resolution. Many practitioners prefer intramuscular triamcinolone 40-80 mg every 6-8 weeks. Oral acitretin has been tried with some success. Many other treatments are of uncertain efficacy because of the lack of randomized controlled trials. For LP of the oral mucosa, topical steroids are usually tried first. Topical and systemic cyclosporin has been tried with some success. Other options include oral or topical retinoids. Even with these effective treatments, relapses are common.

Psoralen with ultraviolet light A (PUVA) therapy for 8 weeks has been reported to be effective. Risks and benefits of this treatment should be considered. PUVA is carcinogenic. Long-term risks include dose-related actinic degeneration, squamous cell carcinoma, and cataracts. A phototoxic reaction with erythema, pruritus, phytophotodermatitis, and friction blisters could occur.

UV-A therapy combined with oral psoralen consists of oral psoralen (0.6 mg/kg), 1.5-2 hours before ultraviolet light, which usually starts at 0.5-1 J/cm$^2$ and is increased by 0.5 J/cm$^2$ per visit. Use of topical ointment at the time of receiving UV-A treatment may decrease the effectiveness of PUVA. Precaution should be taken for persons with a history of skin cancers or hepatic insufficiency.

*Corticosteroids*. These agents have anti-inflammatory properties and cause profound and varied metabolic effects. In addition, these agents modify the body's immune response to diverse stimuli. Topical steroids may be as effective as systemic steroids. Class I or II steroids in ointment form reduce pruritus in cutaneous LP, but they have not been proven to induce remission.

*Retinoids.* These agents modulate cell proliferation. Isotretinoin (Accutane) - oral agent that treats serious dermatologic conditions. Synthetic 13-*cis* isomer of the naturally occurring tretinoin (*trans*-retinoic acid). Both agents are structurally related to vitamin A. Decreases sebaceous gland size and sebum production. May inhibit sebaceous gland differentiation and abnormal keratinization.

*Immunosuppressants*. These agents modulate the immune system. Cyclosporine (Sandimmune, Neoral) - topical treatment under occlusion has been efficacious for genital lesions and may be beneficial in hypertrophic lesions. Mouthwash or oil-

based solutions have been effective for oral LP but seem to be no better than corticosteroids. Systemic treatment has been used for severe resistant cutaneous disease, oral or ulcerative foot involvement, and lichen planopilaris of the scalp. Pediatric population may require higher or more frequent dosing because of accelerated clearance; use with extreme caution.
*Antihistamines.* These agents can reduce pruritus. Hydroxyzine (Atarax, Vistaril) - antagonizes $H_1$- receptors in periphery. Can reduce pruritus and aid in sleep.
**Prognosis:** The prognosis for LP is good, as most cases regress within 18 months. Some cases recur.

## 8.3. Lichen Simplex Chronicus

**Synonyms and related keywords:** neurodermatitis circumscripta, circumscribed neurodermatitis, lichen simplex chronicus of Vidal, LSC, lichen simplex, secondary lichenification, lichen simplex, lichenification.

**Background.**Lichen simplex chronicus (LSC) is thickening of the skin with variable scaling that arises secondary to repetitive scratching or rubbing. LSC is not a primary process. Rather, a person senses pruritus in a specific area of skin (with or without underlying pathology) and causes mechanical trauma to the point of lichenification.
**Pathophysiology.**LSC is found on the skin in regions accessible to scratching. Pruritus provokes rubbing that produces clinical lesions, but the underlying pathophysiology is unknown. Some skin types are more prone to lichenification, such as skin that tends toward eczematous conditions (i.e. atopic dermatitis, atopic diathesis). A relationship likely exists between central and peripheral neural tissue and inflammatory cell products in the perception of itch and ensuing changes in LSC. The possible interplay among primary lesions, psychic factors, and the intensity of pruritus additively influence the extent and severity of LSC.
**Mortality/Morbidity:** No mortality occurs as a result of LSC. Overall, pruritus of LSC is mild to moderate, but paroxysms may occur that are relieved by moderate-to-severe rubbing and scratching. Pruritus is usually described as much worse during periods of inactivity, usually at bedtime and during the night. Touch and emotional stress also may provoke pruritus, which is relieved by moderate-to-severe rubbing and scratching. Lesions cause little direct morbidity; however, occasionally patients report decreased or interrupted sleep, which affects motor and mental functioning. LSC may become secondarily infected after excoriation. LSC is often visible enough to cause patients to seek treatment.
**History.**Patients with LSC usually describe stable pruritic plaques on one or more areas; however, thickening of the skin occurs on any location that the patient can reach, including the following: scalp, nape of neck, extensor forearms and elbows, vulva and scrotum, upper medial thighs, knees, lower legs, and ankles. Erythema is noted most in early lesions. Pruritus is described as worse when patients are still or quiet and as much less or nonexistent when patients are active.Pruritus is usually

intermittent; the resultant scratching provides temporary relief.Patients may have a past medical history of a chronic skin condition or acute trauma. Patients with atopic dermatitis may have LSC in areas of former atopic outbreaks. Sites of irritant or allergic contact dermatitis, insect bites, or other past minor skin trauma sometimes demonstrate pruritus and, subsequently, LSC. Each palm-sized plaque may have 3 zones. A 2- to 3-cm wide peripheral zone that is barely thickened may have isolated papules. The middle zone has lenticular and hemispheric prurigo papules that may be excoriated. The central zone has the greatest thickening and pigmentary alteration.

**Physical.**One or more slightly erythematous, scaly, well-demarcated, lichenified, firm, rough plaques with exaggerated skin lines are noted.Pigmentary changes (especially hyperpigmentation) are seen variably as in any dermatitic lesion.Rubbing plays a key role in lesion formation and is visualized variably by white scratch marks, erosion, and ulceration from deeper scratching.LSC is one of the hyperkeratotic processes from which a cutaneous horn may grow.Patients may scratch lesions de novo when observed. Some patients may start scratching while discussing the itch or describing the lesions.

**Causes.** Atopic dermatitis results in a higher probability of developing LSC. Insect bites, scars (e.g. traumatic, postherpetic/zoster), acne keloidalis nuchae, xerosis, venous insufficiency, and asteatotic eczema are common factors.Psychological factors appear to play a role in the development or exacerbation of LSC.Anxiety has been reported to be more prevalent in patients with LSC. Neurodermatitis is a term formerly used interchangeably with LSC, suggesting a role of anxiety or obsession as part of the pathological process of developing lesions.Lithium has been linked to LSC in one reported case. LSC was dependent on the administration of lithium as evidenced by the observation that the LSC remitted when the medication was discontinued and recurred when it was restarted.Some reserve the diagnosis of lichen simplex for patients who have no known predisposing skin disorder. The term secondary lichenification has been used if the eruption is initiated by a primary dermatosis.

**Lab Studies.** An elevated serum immunoglobulin E level occasionally supports the diagnosis of an underlying atopic diathesis.Perform potassium hydroxide examination and fungal cultures to exclude tinea cruris or candidiasis in patients with genital LSC.

**Other Tests:** Patch testing helps exclude allergic contact dermatitis as an underlying primary dermatosis (e.g. allergic contact dermatitis to nickel with secondary LSC) or as a factor in chronicity (e.g. allergic contact dermatitis to topical corticosteroids used to treat LSC).

**Procedures:** Frequently, skin biopsy is performed to exclude other disorders, particularly psoriasis or mycosis fungoides in elderly patients.

**Histologic Findings:** Histologic examination demonstrates hyperkeratosis, acanthosis, spongiosis, and patches of parakeratosis in the epidermis. Epidermal thickening of all layers is noted, with elongation of rete ridges and with

pseudoepitheliomatous hyperplasia. Papillary dermal fibrosis with vertical streaking of collagen bundles is characteristic.
A characteristic finding of LSC that is noted on electron microscopy is frequent collagen fibers attached to and just above the lamina basalis.
**Medical Care.**Treatment is aimed at reducing pruritus and minimizing existing lesions because rubbing and scratching cause LSC. Topical steroids are the current treatment of choice because they decrease inflammation and itch while concurrently softening the hyperkeratosis. Because lesions are by nature chronic, treatment most likely is lifelong. On larger and more active lesions, a midpotency steroid may be used to treat acute inflammation. Occasionally, occlusion is used to increase potency and enhance delivery of the agent. Occlusion also provides a physical barrier to the scratching. Midpotency topical steroids are not recommended for thin skin (e.g. vulva, scrotum, axilla, face). Direct long-term therapy more at daily use of low-potency nontrophogenic topical corticosteroids. High-potency topical corticosteroids may be used for 3-week courses on thicker-skinned areas.
Oral antianxiety medications and sedation may be considered in certain patients. According to individual need, treatment can be scheduled throughout the day, at bedtime, or both. Antihistamines such as diphenhydramine (Benadryl) and hydroxyzine (Atarax) are common. Doxepin (Sinequan) and clonazepam (Klonopin) may be considered in appropriate cases.Other topical medications reported to decrease pruritus include doxepin cream and capsaicin cream. Both topical and systemic immunomodulators, such as topical tacrolimus, may be used in directing the changes in cellular activity that induce itching and inflammation.
**Prevention.**Direct patients to stop scratching. LSC is worsened or improved depending on the patient's ability to stop scratching.Extremes of temperature and/or humidity, psychic stress, and exposure of previously affected or predisposed areas to cutaneous irritants and allergens provoke relapse.Discussing individual ways to change habitual scratching is helpful.
**Prognosis.**Lesions may clear completely. Pruritus may resolve, but some mild scarring and pigmentary changes remain after successful treatment.Relapse is more likely in periods of psychic stress or if previously affected skin is stressed by extremes of heat or humidity or by skin irritants or allergens.In patients who do not comply with the treatment regimen and scratching cessation, lesions will not improve.

## 8.4. Pityriasis Rosea

**Synonyms and related keywords:** PR, benign papulosquamous disease, herald spot, herald patch

**Background:** Pityriasis rosea (PR) is a common benign papulosquamous disease that was originally described by Camille Melchior Gibert in 1860. Pityriasis

denotes fine scales, and rosea translates as rose colored or pink. PR can have a number of clinical variations. Its diagnosis is important because it may resemble secondary syphilis.

**Pathophysiology:** PR has often been considered to be a viral exanthema. Its clinical presentation supports this concept. PR has been linked to upper respiratory infections, it can cluster within families and close contacts, and it has an increased incidence in individuals who are immunocompromised. As with viral exanthemas, the incidence may increase in the fall and the spring. A single outbreak tends to elicit lifelong immunity.

Immunologic data suggest a viral etiology. Increased amounts of CD4 T cells and Langhans cells are present in the dermis; this observation may indicate viral antigen processing and presentation. Also, anti-immunoglobulin M (IgM) to keratinocytes has been found in patients with PR; this finding may be associated with the exanthema phase of the presumed viral infection.

Despite these tendencies, no single virus has been proven to cause the disease. A number of viruses have been studied for links to PR. Picornavirus-like particles havebeen seen in the tissue of African green monkeys inoculated from human PR lesions. A follow-up study failed to find picornavirus RNA in patients with PR. A recent study showed no increase in anti-IgM to parvovirus B19, making this etiology less likely. Serology and polymerase chain reaction for viral DNA has been negative for Epstein-Barr virus, parvovirus B19, and cytomegalovirus in patients diagnosed with PR.

Other recent work demonstrated human herpesvirus (HHV)–7 viral DNA in both the lesions and the plasma in patients with PR. In addition, a separate study found HHV-7 DNA in lymphocytes in 75% of patients with PR, compared with 9% of controls. Polymerase chain reaction has shown both HHV-7 and HHV-6 DNA in a variety of tissues and secretions from patients with PR. In the same study, in situ hybridization of lesional lymphocytes showed both HHV-7 and HHV-6 mRNA. However, herpesvirus-like particles were not seen via electron microscopy. Follow-up studies have not confirmed a herpes etiology, and because HHV-7 is frequently found in healthy individuals, its etiologic role is controversial.

PR commonly develops in children and young adults, although any age group can be affected. Most patients are aged 10-35 years.

**Causes.**PR may represent a viral exanthema (and at times exanthema). PR-like drug eruptions may be difficult to distinguish. Medication-induced eruptions have been reported with captopril, metronidazole, isotretinoin, penicillamine, levamisole, bismuth, gold, barbiturates, ketotifen, clonidine, and omeprazole. A single case has been reported with terbinafine.Certain vaccinations, such as the BCG vaccine or the diphtheria vaccine, have been reported to cause similar eruptions.Lesions are also thought to be increased in individuals with high stress levels.

**History.**The history should include questions about close contacts with similar eruptions. This finding is uncommon because most cases of PR are sporadic, as PR is thought to reflect a weakly contagious disease. A history of medication intake

should be obtained because several medications have been shown to cause a similar exanthema.

The disease typically begins with a solitary macule that heralds the eruption (called the herald spot/patch), which is usually a salmon-colored macule. This initial lesion enlarges over a few days to become a patch with a collarette of fine scale just inside the well-demarcated border.

Within the next 1-2 weeks, a generalized exanthema usually appears, although it may occur from hours to months after the herald patch. This secondary phase consists of bilateral and symmetric macules with a collarette scale oriented with their long axes along cleavage lines. This phase tends to resolve over the next 6 weeks, but variability is common.Pruritus is common, usually of mild-to-moderate severity, and it occurs in 75% of patients.

**Physical.**The herald patch is usually a single pink patch, 2-10 cm in diameter, on the neck or the trunk with a fine collarette scale. It is observed in more than 50% of patients, and it may occur as multiple lesions or in atypical locations.About 1-2 weeks after the herald patch is seen, the generalized eruption appears, although it has been known to occur from hours to 3 months later. It consists of salmon-colored macules or patches, 0.5-1.5 cm in diameter, with a collarette scale, often described as having a cigarette paper–like appearance. The long axes of the lesions are oriented in a parallel fashion along cleavage lines, giving the classic Christmas tree pattern. These secondary lesions most commonly occur on the trunk, the abdomen, the back, and the proximal upper extremities.Pruritus occurs in 75% of patients and is severe in 25%. Lymphadenopathy is uncommon. Atypical PR occurs in 20% of patients. These variations can be separated into changes in the lesions and/or their distribution. Variable distribution can be difficult to evaluate.Photosensitivity may occur. Photoexacerbated and photoprotected forms have been documented, although photosensitivity is not a classic manifestation of the disease.Lesions may be localized to single areas, such as the abdomen, the groin, the axilla, the distal extremities, the palms, and the soles.

An inverse PR may be seen. This form manifests as lesions on the face and the distal extremities, and it is more common in children than in adults. The herald patch may be the only manifestation of the disease.A unilateral variant in which the lesions do not cross the midline has been described.Drug-induced cases are frequently observed without the herald patch. Variations in lesion morphology are noteworthy. Atypical, large patches tend to be fewer in number. They may coalesce to form a variant known as pityriasis circinata et marginata of Vidal. The primary lesions may be papules, vesicles, pustules, or urticarial or purpuric plaques. PR may first be evident with widespread, intensely pruritic papulovesicles in an unusual distribution, such as on the neck and the scalp.Papular PR tends to have scaling papules in the normal distribution; this form is more common in children than in adults.Erythema multiforme–like plaques may be evident. Oral involvement may occur as punctate hemorrhages, ulcers, papulovesicles, bullae, or erythematous plaques. Most studies find the incidence to be less than 10%; however, one study reported them in as many as 16% of patients.Purpuric PR is

seen in both adults and children, and it follows the usual presentation of the disease.

**Lab Studies.**One must be careful to rule out syphilis. A screening rapid plasma reagin (RPR) test or a Venereal Disease Research Laboratory (VDRL) test should be ordered for appropriate individuals.One should be aware of the prozone phenomenon seen in secondary syphilis and request titration of the RPR test.An HIV test should also be considered in these patients. Other laboratory tests are usually normal and, therefore, unhelpful. Changes in the white blood cell count and differential, as well as increases in erythrocyte sedimentation rate, total serum protein level, globulin level, and albumin level, are rarely reported.

**Histologic Findings.**A biopsy specimen is helpful to confirm the diagnosis, especially in atypical cases. It shows superficial perivascular dermatitis. Focal parakeratosis in mounds, hyperplasia, and focal spongiosis are observed in the epidermis. The epidermis may show exocytosis with lymphocytes, variable spongiosis, mild acanthosis, and a thinned granular layer. In the dermis, extravasated red blood cells are a helpful finding along with a perivascular infiltrate of lymphocytes, histiocytes, and eosinophils. A number of monocytes are also commonly present.

The herald patch has similar features but has a deeper infiltrate and more acanthosis owing to its chronicity. Such variations as dyskeratotic cells in the epidermis, multinuclear giant cells, and focal acantholytic dysfunction have been observed. These features may closely resemble erythema annulare centrifugum, guttate psoriasis, superficial gyrate erythema, and small plaque parapsoriasis.

**Medical Care.**The most important part of treating patients with PR is reassurance that the rash will resolve. Relief of pruritus is helpful and can be accomplished by using topical steroids, oral antihistamines, topical menthol-phenol lotions, and oatmeal baths. Systemic steroids are not recommended. Although they suppress pruritus, systemic steroids do not shorten the overall disease; in fact, they may prolong or exacerbate the disease.Ultraviolet B (UV-B) light therapy, starting at 80% of the minimum erythrogenic dose, may rapidly relieve pruritus in resistant cases. If itching is not controlled, the dose of UV-B light should be increased by 20% until symptoms decrease. However, a recent study failed to find improvement in the pruritus but did note decreased lesion severity with UV-B light therapy. One must take into consideration the possibility of postinflammatory pigmentation with light therapy.For vesicular PR, a single case was considerably improved with 20 mg of dapsone twice a day.

**Prognosis:** The prognosis for PR is excellent. Patients may return to work or school because they are not considered to be contagious.

# IX. BACTERIAL INFECTIONS

## 9.1. Ecthyma

**Synonyms and related keywords:** ulcerative pyoderma, cutaneous pyoderma, impetigo, deep impetigo

**Background.** Ecthyma is an ulcerative pyoderma of the skin caused by group A beta-hemolytic streptococci. Because ecthyma extends into the dermis, it is often referred to as a deeper form of impetigo. Ecthyma has a predilection for children and elderly individuals.

**Pathophysiology.** Ecthyma begins similarly to superficial impetigo. Group A beta-hemolytic streptococci may initiate the lesion or may secondarily infect preexisting wounds. Preexisting tissue damage (e.g. excoriations, insect bites, dermatitis) and immunocompromised states (e.g. diabetes, neutropenia) predispose patients to the development of ecthyma. Spread of skin streptococci is augmented by crowding and poor hygiene.

**Causes.** Ecthyma can be seen in areas of previously sustained tissue injury (e.g. excoriations, insect bites, dermatitis).Ecthyma can be seen in patients who are immunocompromised (e.g. diabetes, neutropenia).Important factors contribute to the development of streptococcal pyodermas or ecthyma (high temperature and humidity, crowded living conditions, poor hygiene).Untreated impetigo that progresses to ecthyma most frequently occurs in patients with poor hygiene.

**History.** Ecthyma usually arises on the lower extremities of children, persons with diabetes, and neglected elderly patients.During wartime in tropical climates, ecthymatous ulcers are commonly found on the ankles and dorsa of the feet.

**Physical.** Ecthyma begins as a vesicle or pustule overlying an inflamed area of skin that deepens into a dermal ulceration with overlying crust.The crust is gray-yellow and is thicker and harder than the crust of impetigo.A shallow, punched-out ulceration is apparent when adherent crust is removed.The deep dermal ulcer has a raised and indurated surrounding margin. Ecthyma lesions can remain fixed in size (sometimes resolving without treatment) or can progressively enlarge to 0.5-3 cm in diameter.Ecthyma heals slowly and commonly produces a scar. Regional lymphadenopathy is common, even with solitary lesions.

**Complications.** Ecthyma rarely produces systemic symptoms. Invasive complications of streptococcal skin infections include cellulitis, erysipelas, gangrene, lymphangitis, suppurative lymphadenitis, and bacteremia.Non-suppurative complications of streptococcal skin infections include scarlet fever and acute glomerulonephritis. Prompt antibiotic therapy does not appear to reduce the rate of poststreptococcal glomerulonephritis.Possible sequelae of secondary untreated *S. aureus* pyodermas include cellulitis, lymphangitis, bacteremia, osteomyelitis, and acute infective endocarditis. Some *S. aureus* strains produce exotoxins that can lead to staphylococcal scalded skin syndrome and toxic shock syndrome.

**Lab Studies.** Gram stain and culture of ecthyma lesions reveal gram-positive cocci that represent group A streptococci, with or without *Staphylococcus aureus*. Prior group A streptococci infection can be detected by anti-DNase beta testing.
**Histologic Findings.** Ecthyma lesions show dermal necrosis and inflammation. A deep and superficial granulomatous perivascular infiltrate occurs along with endothelial edema. A heavy crust covers the surface of the ecthyma ulcer.
**Medical Care.** Medical treatment depends on the progression of the lesions. Hygiene is important. Maintain cleanliness by using bactericidal soap and frequently changing bed linens, towels, and clothing. Remove crusts and apply an antibiotic ointment daily. Consider topical therapy with mupirocin ointment for localized ecthyma. More extensive lesions require oral antibiotics; the duration of treatment varies because ecthyma may require several weeks of therapy to completely resolve.Oral antistaphylococcal agents (e.g. dicloxacillin, cephalexin, erythromycin, clindamycin) have been used in the presence of possible secondary *S. aureus* infections. Penicillin should be adequate to treat ecthyma.Consider parenteral antibiotics for widespread involvement.
**Prognosis.** Ecthyma lesions are slow to heal but do respond to appropriate antibiotics over several weeks; prognosis is favorable.

## 9.2. Impetigo

**Synonyms and related keywords:** impetigo contagiosa, Fox impetigo, impetigo bullosa, impetigo contagiosa bullosa, impetigo neonatorum

**Background.**Impetigo is a highly contagious gram-positive bacterial infection of the superficial layers of the epidermis. The 2 forms of the disease, bullous and non-bullous (crusted) impetigo, are caused by *Staphylococcus aureus* and group A beta-hemolytic streptococci (GABHS). Both organisms can be present at the same time. It has been suggested that infection by *S. aureus* is preceded by a primary infection by GABHS.
Impetigo presents as either a primary pyoderma of intact skin or a secondary infection of preexisting skin disease or traumatized skin. Impetigo rarely progresses to systemic infection, although poststreptococcal glomerulonephritis is a rare complication.
**Bullous impetigo** (least common). The causative agent of bullous impetigo is gram-positive, coagulase-positive, group II *S. aureus*, most often phage type 71. Approximately 30% of the population is colonized in the anterior nares by this bacterium. Some individuals colonized by *S. aureus* experience recurrent episodes of impetigo on the nose and lip. Bacteria can spread from the nose to normal skin within 11 days, with impetigo lesions appearing 11 days later.
A small percentage of individuals are colonized in the axillae, pharynx, hands, and perineum. Individuals who are permanent carriers serve as a reservoir of the infection for other people. Most healthy persons harbor the organism as an

occasional transient part of their microbial flora. Patients with atopic dermatitis more commonly have skin colonized by *S. aureus*.
The organism often passes from one individual to another through hand contact, entering through non-intact skin created by cutaneous diseases (e.g. atopic dermatitis, dermatophytosis, varicella, herpes simplex), thermal burns, surgery, trauma, radiation therapy, or insect bites. Immunosuppression by medications (e.g. systemic corticosteroids, oral retinoids, chemotherapy), systemic diseases (e.g. HIV infection, diabetes mellitus), intravenous drug abuse, and dialysis also encourage bacterial growth.
*S. aureus* produces the extracellular exfoliative exotoxins termed exfoliatins A and B. These molecules are superantigens that act locally and activate T lymphocytes. The toxins produce a cleavage in the upper epidermis, either within the stratum granulosum or immediately below it. Coagulase produces fibrin thrombi that may cause the toxins to remain localized within the upper epidermis.
**Non-bullous impetigo**. Studies have shown that in industrialized nations, GABHS and *S. aureus* occur with equal frequency as the causative agents for non-bullous impetigo. In developing nations, GABHS is the more common cause.
*S. aureus* produces bacteriotoxins toxic to streptococci. These bacteriotoxins may be the reason that only *S. aureus* is isolated in lesions that are caused predominantly by streptococci. If an individual is in close contact with others (e.g. household members, classmates, teammates) who have GABHS skin infection or who are carriers of the organism, colonization of normal skin of that individual may result. Once the normal skin is colonized, minor trauma, such as abrasions or insect bites, may result in the development of impetigo lesions within 1-2 weeks.
GABHS can be detected in the nose and throat of some individuals 2-3 weeks after lesions develop, although they do not have symptoms of streptococcal pharyngitis.
**History.** Bullous impetigo begins as a rapid onset of blisters that enlarge and rupture. Lesions are asymptomatic. Occasionally, patients complain of pain or itching. Individuals with impetigo frequently recall exposure to a person who is a known carrier of *S. aureus* or streptococcal organisms or who has a pyoderma.Hot humid weather, participation in contact sports, crowded living conditions, poor personal hygiene, or an unhygienic work environment encourage contamination of the skin by pathogenic bacteria that can cause impetigo.A compromised immune system resulting from disease or disease treatment (e.g. HIV, AIDS, posttransplantation, insulin-dependent diabetes, hemodialysis, chemotherapy, radiation therapy, systemic corticosteroids), intravenous drug abuse, cutaneous conditions (e.g. atopic dermatitis, dermatophytosis, varicella, herpes simplex), recent surgical wounds, insect bites, thermal burns, or abrasions creates an environment conducive to bacterial infection.Symptoms of a sore throat or fever usually are not present. Hot and humid environments with crowded living conditions and poor hygiene are associated with non-bullous impetigo.
**Physical.*Bullous impetigo***. The characteristic lesion is a vesicle that develops into a superficial flaccid bulla less than 1 cm in diameter on intact skin, with minimal or no surrounding redness. Initially, the vesicle contains clear fluid that becomes

turbid.The roof of the bulla ruptures, often leaving a peripheral collarette of scale or a tube-like rim at the periphery. A varnish-like crust develops centrally, which if removed, reveals a moist red base.Intact bullae usually are not present. When present, intact bullae do not demonstrate a positive Nikolsky sign. Lesions of a primary skin disease, such as atopic dermatitis or varicella, may be present.Lesions may be localized or scattered widely. Lesions often are found on the face but may appear anywhere on the body.No regional lymphadenopathy is present. Rarely, infants may present with signs of pneumonia, septic arthritis, or osteomyelitis.

***Non-bullous impetigo.*** The characteristic lesion is a fragile vesicle or pustule that readily ruptures and becomes a honey-yellow, adherent, crusted papule or plaque of less than 2 cm and with minimal or no surrounding redness.Lesions develop on either normal or traumatized skin or are superimposed on a preexisting skin condition (e.g. scabies, varicella, atopic dermatitis).Lesions are located around the nose, mouth, and exposed parts of the body (e.g. arms, legs), sparing the palms and soles.Localized lymphadenopathy usually is present, and nodes may be tender.If left untreated, lesions spread by autoinoculation then spontaneously resolve after a few weeks. Individual lesions resolve within 10-15 days.Rarely, pedal edema and hypertension may be noted in an individual with non-bullous impetigo. Both are signs of renal dysfunction most likely resulting from glomerulonephritis.No signs of pharyngitis are present.

**Complications.**Rarely, lesions resolve with scarring and postinflammatory hyperpigmentation or hypopigmentation. Bullous impetigo: cellulitis, lymphangitis, bacteremia with subsequent pneumonitis, septic arthritis, osteomyelitis, and septicemia may develop.Non-bullous impetigo: acute glomerulonephritis develops in 2-5% of individuals with impetigo, most often in children aged 2-4 years. Onset usually is 10 days after impetigo lesions first appear, but it can occur from 1-5 weeks later. Transient proteinuria and hematuria may occur during impetigo and resolve before renal involvement develops.Ecthyma, scarlet fever, erysipelas, cellulitis, lymphangitis and, rarely, bacterial endocarditis may develop.

**Lab Studies.** Impetigo usually is diagnosed clinically. Bacterial culture and sensitivity are recommended if standard topical or oral treatment does not result in improvement.Urinalysis is necessary to evaluate for acute poststreptococcal glomerulonephritis if the patient develops new onset edema or hypertension. Hematuria, proteinuria, and cylindruria are indicators of renal involvement.A potassium hydroxide wet mount may be performed to exclude bullous dermatophyte infection.A Tzanck preparation or viral culture may be performed to exclude herpes simplex infection.A bacterial culture of the nares may be obtained to determine whether a patient is an *S. aureus* carrier.If the nares culture is negative and the patient has persistent recurrent episodes of impetigo, bacterial cultures should be obtained from the axilla, pharynx, and perineum.

**Histologic Findings.**Both bullous and non-bullous impetigo show a vesicopustule in the upper epidermis, either within the stratum granulosum, above it, or below it. Occasionally, gram-positive cocci are found within the vesicopustule.

In bullous impetigo, few or no inflammatory cells are present within the bulla. A polymorphous infiltrate is present in the upper dermis. In non-bullous impetigo, neutrophils are present within the vesicopustule. Epidermal spongiosis with neutrophils and a severe dermal infiltrate of neutrophils and lymphoid cells are seen.

**Medical care.** Topical antibiotics are applied bid/tid. Oral antibiotics with appropriate bacterial coverage are used in individuals with extensive impetigo or who are refractory to topical treatment. Gentle debridement of lesional crusts with a washcloth and antibacterial soap is recommended.

The goal of pharmacotherapy is to reduce morbidity, to prevent complications, and to prevent spread to other individuals. Antimicrobial therapy must cover all likely pathogens in the context of the clinical setting. Topical antibiotic ointments active against *S. aureus* and streptococci are used most commonly. Mupirocin applied topically has been shown to be as effective as oral antibiotics. At times, systemic antibiotic treatment is indicated against gram-positive bacteria for extensive cutaneous infections or for cases with systemic manifestations (e.g. septic arthritis). Penicillin resistance is common, and penicillinase-resistant penicillins are recommended. Erythromycin resistance is present in some geographic areas.

If pruritus is significant, antihistamines can be prescribed to minimize scratching. Avoidance of trauma to the skin may prevent or limit the spread of impetigo by autoinoculation.

**Prevention.** Treat traumatized skin with an over-the-counter triple-antibiotic ointment that contains bacitracin, Polysporin, and neomycin (applied bid).Evaluate hospital nursery staff and household members for pyodermas or asymptomatic bacterial carrier states.Treat preexisting underlying skin diseases, such as atopic dermatitis. Antihistamines and topical steroids help decrease scratching.Teach good personal hygiene (e.g. trim nails frequently, keep nails short and clean, wash hands frequently).For patients with recurrent impetigo or for *S. aureus* nasal carriers, prescribe 2% mupirocin cream or ointment (Bactroban) inside nostrils tid for 5 days each month to reduce colonization in the nose. In addition, encourage patients to use antibacterial soap.Patients who are chronic nasal carriers also can be treated with rifampin. Advise patients about improving environmental conditions through the addition of air conditioning and by keeping surroundings clean.

**Prognosis.**Spontaneous healing rarely occurs. If left untreated, some lesions may resolve spontaneously, while new lesions appear elsewhere on the body.Resolution of lesions usually occurs after 7-10 days of treatment.

## 9.3.Pyoderma Vegetans

**Synonyms and related keywords:** PV, blastomycosis-like pyoderma, mycosis-like pyoderma

**Background:** Pyoderma vegetans (PV) is a rare disorder clinically characterized by large verrucous plaques with elevated borders and multiple pustules. PV is an eruption of multiple pustular ulcerations; it may have a bacterial etiology similar to chancriform pyoderma.

**Pathophysiology.**The etiology of PV is not known. An immunosuppressive state or a dysfunction of the immune system is believed to cause the development of vegetations. Diffuse T-cell lymphoma, ulcerative colitis, and HIV infection have been associated with this condition.

**Physical:** Both clinical and histologic findings are necessary to make the diagnosis of PV. At clinical examination, multiple pustules and large verrucous plaques with an elevated border are identified.At histologic examination, pseudoepitheliomatous hyperplasia is demonstrated.

**Lab Studies.** Pathogenic organisms, such as *Staphylococcus aureus,* are grown from wound cultures, and cultures should also be taken for fungi and mycobacteria.Direct and indirect immunofluorescence can aid in differentiating PV and pemphigus vegetans.Hidradenitis suppurativa may cause an immune complex deposition in the skin, which precipitates the PV reaction. This reaction can be seen as a nonspecific immunoreactant deposition with direct immunofluorescence.

**Histologic Findings.**Two predominant features are found in PV: pseudocarcinomatous hyperplasia and numerous abscesses in both the hyperplastic epidermis and the dermis. The abscesses can be made up of neutrophils or eosinophils.

**Medical Care.**No standardized treatment plan is available for PV, although antibiotic treatment has often been used with variable results. Topical wound care with copper sulfate or aluminum subacetate dressings and intravenous antibiotics successfully treated patients with PV.Topical aluminum acetate soaks with intravenous ceftriaxone had moderate success at clearing PV in another patient.Antibiotic treatment has been successfully supplemented with laser debridement or curettage to clear lesions.

**Prognosis.**With therapy, the prognosis is good, although this may prove untrue in the face of associated medical conditions, such as HIV, diffuse T-cell lymphoma, and CML, which must be properly addressed.

## 9.4. Staphylococcal Scalded Skin Syndrome

**Synonyms and related keywords:** SSSS, exfoliative dermatitis, toxin-mediated staphylococcal syndromes, *Staphylococcus aureus*

**Background.**Staphylococcal scalded skin syndrome (SSSS) is a toxin-mediated type of exfoliative dermatitis. Toxin-mediated staphylococcal syndromes comprise a group of blistering skin diseases, ranging in severity from localized bullous impetigo to SSSS, in which superficial blistering and exfoliation follow widespread painful erythema.

**Pathophysiology.**The disorder is caused by toxigenic strains of *Staphylococcus aureus,* usually belonging to phage group 2 (types 3A, 3B, 3C, 55, or 71). Two exotoxins (ET), epidermolytic toxin A (ET-A) and epidermolytic toxin B (ET-B), are responsible for the pathologic changes seen in SSSS. Both toxins produce blistering by disruption of the epidermal granular cell layer, apparently from direct effects on desmosomes; this disruption leads to interdesmosomal splitting. The toxins most likely bind directly to the desmosomal protein desmoglein-1, but the mechanism of action of the toxin is not fully understood.

An asymptomatic adult carrier introduces the causative bacteria into the nursery. Asymptomatic nasal carriage of *S. aureus* occurs in 20-40% of healthy individuals, with the organism being isolated from the hands, the perineum, and the axillae in a smaller proportion of the general population.

**Frequency.** SSSS most commonly occurs in infants and in young children, and it tends to occur in outbreaks in neonatal nurseries or in day care nurseries. Large outbreaks of SSSS in neonatal nurseries have been described, but the occurrence of SSSS in adults as a nosocomial infection appears to be exceptional; epidemics have never been observed.

**Mortality/Morbidity.**Children generally do well and are not as ill as their dramatic eruptions might suggest. SSSS is usually associated with a trivial infective focus in the conjunctivae or the skin; however, severe infections, such as sepsis, do contribute to a low but appreciable fatality rate (3%). Morbidity in the occasional child who develops cellulitis, sepsis, and pneumonia can be significant.In children, the foci of staphylococcal infections are usually the nasopharynx or localized skin infections.Adults with SSSS often have blood cultures positive for toxigenic *S. aureus,* and mortality rates can be high (>50%).

**Age.** The disease most commonly affects children younger than 5 years, particularly neonates. A decreased ability to achieve renal clearance of toxins and a lack of specific immunity (antibody) to the toxins make neonates the group at highest risk.Older children and adults may also develop the disease. In such cases, renal insufficiency or immunodeficiency (e.g. HIV infection) appears to explain the susceptibility to the syndrome. Adults who are affected range in age from 19-91 years, with one half of the cases occurring in adults older than 60 years.

**History.**SSSS originates from a focus of infection that may be a purulent conjunctivitis, otitis media, or occult nasopharyngeal infection.It usually begins with fever; irritability; and a generalized, faint, orange-red, macular erythema with cutaneous tenderness.Periorificial and flexural accentuation may be observed. A positive Nikolsky sign (slippage of the superficial layer of the epithelium on gentle pressure) can often be elicited at this stage.

**Physical.**Within 24-48 hours, the rash progresses from a scarlatiniform to a blistering eruption.Characteristic tissue paper–like wrinkling of the epidermis is followed by the appearance of large, flaccid bullae in the axillae, in the groin, and around the body orifices.Subsequent generalized involvement occurs elsewhere on the body, but infection spares the mucous membranes.As sheets of epidermis are shed, a moist erythematous base is revealed. Despite the dramatic clinical picture,

the entire process usually subsides with superficial desquamation, and healing is usually complete within 5-7 days.Cultures obtained from intact bullae are usually sterile; this finding is consistent with hematogenous dissemination of a toxin produced at a distant focus of staphylococcal infection.An abortive form of SSSS, known as the scarlatiniform variant, shows the early erythrodermic and final desquamative stages seen in SSSS, but the bullous stage does not occur.Other intermediate forms of scalded skin syndrome begin as localized bullous impetigo, but they evolve to produce regionally limited bullae and denuded areas that may or may not harbor staphylococci.

**Complications.**Cellulitis, sepsis, and pneumonia are possible complications that may occur in children with SSSS.

**Lab Studies.**The definitive diagnosis depends on culture and biopsy results. Perform culturing in all patients with suspected SSSS for identification and antibiotic sensitivities of the causative organism.Investigate the possibility of a staphylococcal carrier in the vicinity.

**Histologic Findings.**All forms of scalded skin syndrome are characterized by intraepidermal cleavage, with splitting that occurs beneath and within the stratum granulosum. The cleavage space may contain free-floating or partially attached acantholytic cells. The remainder of the epidermis appears unremarkable, and the dermis contains no inflammatory cells.

**Medical Care.**Direct the therapy for scalded skin syndrome toward eradication of the staphylococcal focus of infection, which generally requires intravenous, penicillinase-resistant, antistaphylococcal antibiotics. The current treatment of choice is cloxacillin.Oral antibiotic therapy can be substituted within several days or sooner. Antibiotics, supportive care, and appropriate attention to fluid and electrolyte management because of disrupted epidermal barrier function usually ensure rapid recovery.Recognizing the potential for epidemic scalded skin syndrome in neonatal care units is important.Identification of health care workers colonized or infected with toxigenic *S. aureus* is an integral part of managing the problem.Apply control measures, including strict enforcement of chlorhexidine hand washing, administration of an oral antibiotic therapy for workers who are infected, and application of mupirocin ointment for eradication of persistent nasal carriage.

**Prognosis.**The prognosis of the disease is good in children, and the mortality rate is low if they are treated.In adult cases of SSSS, the mortality rate is high despite appropriate antibiotic therapy.

# X. BULLOUS DISEASES

Speaking about bullous dermatoses we refer to a group of severe autoimmune conditions with a chronic, partially life-threatening course. The term "bullous" comes from the leading symptom of these conditions which is a bulla or a blister resulting from pathogenic autoimmune reactions occurring in the epidermis or the basal membrane zone.

## 10.1. Pemphigus Vulgaris

**Synonyms and related keywords:** PV, bullous disease

**Background.**Pemphigus is derived from the Greek word *pemphix* meaning bubble or blister. Pemphigus describes a group of chronic bullous diseases, originally named by Wichman in 1791. The term pemphigus once included most bullous eruptions of the skin, but diagnostic tests have improved, and bullous diseases have been reclassified.

The term pemphigus refers to a group of autoimmune blistering diseases of the skin and mucous membranes characterized histologically by intradermal blister and immunopathologically by the finding of in vivo bound and circulating immunoglobulin G (IgG) antibody directed against the cell surface of keratinocytes. The 3 primary subsets of pemphigus include pemphigus vulgaris (PV), pemphigus foliaceus, and paraneoplastic pemphigus. Each type of pemphigus has distinct clinical and immunopathologic features. PV accounts for approximately 70% of pemphigus cases.

**Pathophysiology.**PV is an autoimmune, intraepithelial, blistering disease affecting the skin and mucous membranes and is mediated by circulating autoantibodies directed against keratinocyte cell surfaces. In 1964, autoantibodies against keratinocyte surfaces were described in patients with pemphigus. Clinical and experimental observations indicate that the circulating autoantibodies are pathogenic. An immunogenetic predisposition is well established.

Blisters in PV are associated with the binding of IgG autoantibodies to keratinocyte cell surface molecules. These intercellular or PV antibodies bind to keratinocyte desmosomes and to desmosome-free areas of the keratinocyte cell membrane. The binding of autoantibodies results in a loss of cell-cell adhesion, a process termed acantholysis.

PV antigen: Intercellular adhesion in the epidermis involves several keratinocyte cell surface molecules. Pemphigus antibody binds to keratinocyte cell surface molecules desmoglein 1 and desmoglein 3. The binding of antibody to desmoglein may have a direct effect on desmosomal adherens or may trigger a cellular process that results in acantholysis. Antibodies specific for non-desmosomal antigens also have been described in the sera of patients with PV; however, the role of these antigens in the pathogenesis of disease is not known.

Antibodies: patients with active disease have circulating and tissue-bound autoantibodies of both the immunoglobulin G1 (IgG1) and immunoglobulin G4 (IgG4) subclasses. Disease activity correlates with antibody titer in most patients.
Complement: pemphigus antibody fixes components of complement to the surface of epidermal cells. Antibody binding may activate complement with the release of inflammatory mediators and recruitment of activated T cells.
Disease association: pemphigus occurs in patients with other autoimmune diseases, particularly myasthenia gravis and thymoma.
**Frequency.**PV is uncommon, and the exact incidence and prevalence depends on the population studied. PV has been reported to occur worldwide. PV incidence varies from 0.5-3.2 cases per 100,000. PV incidence is increased in patients of Ashkenazi Jewish descent.
**Mortality/Morbidity.**The mortality rate for PV is approximately 5-15%. Complications secondary to the use of high-dose corticosteroids contribute to the mortality rate. Morbidity and mortality are related to the extent of disease, the maximum dose of systemic steroids required to induce remission, and the presence of other diseases. Prognosis is worse in patients with extensive disease and in older patients. PV involves mucosa in 50-70% of patients. This may limit oral intake secondary to dysphagia. Blistering and erosions secondary to the rupture of blisters may be painful and limit the patient's daily activities. Patients with PV typically heal without scarring unless the disease is complicated by severe secondary infection.
**Age.**Mean age of onset is approximately 50-60 years; however, the range is broad, and disease onset in older individuals and in children has been described. Patients are younger at presentation in India than in Western countries.
**Causes.**The cause of PV remains unknown; however, several potentially relevant factors have been identified. Genetic factors: predisposition to pemphigus is linked to genetic factors. Certain major histocompatibility complex (MHC) class II molecules, in particular alleles of human leukocyte antigen DR4 (DRB1*0402) and human leukocyte antigen DRw6 (DQB1*0503), are common in patients with PV.
**CLINICAL.** Mucous membranes: PV presents with oral lesions in 50-70% of patients, and almost all patients have mucosal lesions. Mucosal lesions may be the sole sign for an average of 5 months before skin lesions develop, or they may be the sole manifestation of the disease.
Skin: most patients develop cutaneous lesions. The primary lesion of PV is a flaccid blister, which usually arises on normal-appearing skin but may be found on erythematous skin. New blisters usually are flaccid or become flaccid quickly. Affected skin often is painful but rarely pruritic.
***Drug-induced PV***: drugs reported most significantly in association with PV include penicillamine, captopril, and other thiol-containing compounds.
**Physical:** Mucous membranes typically are affected first in PV. Mucosal lesions may precede cutaneous lesions by months. Patients with mucosal lesions may present to dentists, oral surgeons, or gynecologists.

*Mucous membranes*. Intact bullae are rare in the mouth. More commonly, patients have ill-defined, irregularly shaped, gingival, buccal or palatine erosions, which are painful and slow to heal. The erosions extend peripherally with shedding of the epithelium.The mucous membranes most often affected are those of the oral cavity, which is involved in almost all patients with PV and sometimes is the only area involved. Erosions may be seen on any part of the oral cavity. Erosions can be scattered and often extensive. Erosions may spread to involve the larynx with subsequent hoarseness. The patient often is unable to eat or drink adequately because the erosions are so uncomfortable.

Other mucosal surfaces may be involved, including the conjunctiva, esophagus, labia, vagina, cervix, penis, urethra, and anus.

*Skin*: the primary lesion of PV is a flaccid blister filled with clear fluid that arises on normal skin or on an erythematous base. The blisters are fragile; therefore, intact blisters may be sparse. The contents soon become turbid, or the blisters rupture producing painful erosions, which is the most common skin presentation. Erosions often are large because of their tendency to extend peripherally with the shedding of the epithelium.

***Vegetating PV***: Ordinary PV erosions may develop vegetation. Lesions in skin folds readily form vegetating granulations. In some patients, erosions tend to develop excessive granulation tissue and crusting, and these patients display more vegetating lesions. This type of lesion tends to occur more frequently in intertriginous areas and on the scalp or face. The vegetating type of response can be more resistant to therapy and can remain in one place for long periods of time.

Nails: acute paronychia, subungual hematomas, and nail dystrophies have been reported with PV.

***Pemphigus in pregnancy***: Occurrence in pregnancy is rare. When present, maternal autoantibodies may cross the placenta, resulting in neonatal pemphigus. Neonatal pemphigus is transient and improves with clearance of maternal autoantibodies.

Nikolsky sign: In patients with active blistering, firm sliding pressure with a finger separates normal-appearing epidermis, producing erosion. This sign is not specific for PV and is found in other active blistering diseases.

Asboe-Hansen sign: Lateral pressure on the edge of a blister may spread the blister into clinically unaffected skin.

**Complications.**Secondary infection, which may be either systemic or localized to the skin, may occur because of the use of immunosuppressants and the presence of multiple erosions. Cutaneous infection delays wound healing and increases the risk of scarring.Malignancies resulting from immunosuppressants have been reported. Growth retardation has been reported in children taking systemic corticosteroids and immunosuppressants.Bone marrow suppression has been reported in patients receiving immunosuppressants. Increased incidence is reported of leukemia and lymphoma in patients receiving prolonged immunosuppression.Impaired immune responsiveness caused by corticosteroids and other immunosuppressive drugs may result in the rapid spread of infection. Corticosteroids suppress clinical signs of

infection and may allow diseases such as septicemia or tuberculosis to reach an advanced stage before diagnosis.Osteoporosis may occur following the use of systemic corticosteroids. Adrenal insufficiency has been reported following prolonged use of glucocorticoids.

**Lab Studies.** To establish a diagnosis of PV, perform the following tests:

Histopathology from the edge of a blister

Direct immunofluorescence (DIF) on normal-appearing perilesional skin

Indirect immunofluorescence (IDIF) using the patient's serum if DIF is positive. The preferred substrate for IDIF is monkey esophagus or salt-split normal human skin substrate.

DIF demonstrates in vivo deposits of antibodies and other immunoreactants, such as complement. DIF usually shows IgG deposited on the surface of the keratinocytes in and around lesions. IgG1 and IgG4 are the most common subclasses. Complement components such as C3 and immunoglobulin M are present less frequently than IgG. DIF shows intercellular deposition throughout the epidermis. This pattern of immunoreactants is not specific for PV and may be seen in pemphigus vegetans, pemphigus foliaceus, and pemphigus erythematosus. The best location for DIF is normal perilesional skin. When DIF is performed on lesional skin, false-positive results can be observed.

Skin biopsy specimens placed in transport media may yield false-negative results; therefore, fresh tissue is the preferred substrate for DIF studies.

In the patient's serum, IDIF demonstrates the presence of circulating IgG autoantibodies that bind to epidermis. Circulating intercellular antibodies are detected using IDIF in 80-90% of patients with PV. The titer of circulating antibody correlates with disease course.

**Histologic Findings.**Histopathology demonstrates an intradermal blister. The earliest changes consist of intercellular edema with loss of intercellular attachments in the basal layer. Suprabasal epidermal cells separate from the basal cells to form clefts and blisters. Basal cells are separated from one another and stand like a row of tombstones on the floor of the blister, but they remain attached to the basement membrane. Blister cells contain some acantholytic cells. Histopathology can help differentiate PV from pemphigus foliaceous, which demonstrates a more superficial epidermal cleavage.

Tzank preparation is a smear taken from the base of a blister or oral erosion that contains acantholytic cells. Blistering is preceded by eosinophilic spongiosis in some patients. The superficial dermis has a mild, superficial, mixed inflammatory infiltrate, which includes some eosinophils.

## TREATMENT

**Medical Care.**The aim of treatment in PV is the same as in other autoimmune bullous diseases, which is to decrease blister formation, promote healing of blisters and erosions, and determine the minimal dose of medication necessary to control the disease process. Therapy must be tailored for each patient, taking into account preexisting and coexisting conditions. Patients may continue to experience mild disease activity while under optimal treatment.

## MEDICATION

The aim of treatment is to reduce inflammatory response and autoantibody production. While target-specific therapy is not available, non-target–specific treatments currently are used. The most commonly used medications are corticosteroids. The introduction of corticosteroids has reduced mortality greatly, but significant morbidity remains. Numerous steroid regimens with or without immunosuppressive agents have been recommended. Immunosuppressants should be prescribed and monitored by physicians familiar with these agents. Wound care of erosions includes daily gentle cleaning, application of topical agents to promote wound healing, and use of non-adhesive dressings. The goal of wound care is to promote healing, minimize trauma to the surrounding skin, and diminish scarring.

Useful adjuvants in patients with PV with generalized disease unresponsive to steroids and/or other anti-inflammatory agents or in patients unable to tolerate prednisone. Azathioprine (Imuran) - antagonizes purine metabolism and inhibits synthesis of DNA, RNA, and proteins. May decrease proliferation of immune cells, which results in lower autoimmune activity. In conjunction with prednisone, it is more effective than prednisone alone. May be an effective monotherapy in mild cases, although the therapeutic effect is delayed 3-5 weeks. Consider withdrawal if there is no improvement within 3 months.

**Consultations.**Management of patients with PV requires coordination of care between the dermatologist and the patient's primary care physician. An ophthalmologist should evaluate patients with suspected ocular involvement and those requiring prolonged high-dose steroids.Patients with oral disease may require a dentist and/or an otolaryngologist for evaluation and care.Patients on systemic steroids should maintain adequate vitamin D and calcium intake through diet and supplements. Patients with a history of renal calculi should not receive calcium carbonate.Patients receiving long-term systemic corticosteroids may require an endocrinologist (prophylaxis or treatment of osteoporosis).

**Diet.**No dietary restrictions exist, but patients with oral disease may benefit from avoiding foods, such as spicy foods, tomatoes, orange juice, and hard foods that may traumatize the oral epithelium mechanically, such as nuts, chips, and hard vegetables and fruit.

**Activity.**Advise patients to minimize activities that traumatize the skin and that may precipitate blistering, such as contact sports. Nontraumatic exercises, such as swimming, may be helpful.Dental plates, dental bridges, or contact lenses may precipitate or exacerbate mucosal disease.

**Prognosis.**The severity and natural history of PV are variable, but before the advent of steroids, most patients with PV died. Treatment with systemic steroids has reduced the mortality rate to 5-15%.Most deaths occur during the first few years of disease, and if the patient survives 5 years, the prognosis is good. Early disease probably is easier to control than widespread disease, and mortality may be higher if therapy is delayed.Morbidity and mortality are related to the extent of disease, the maximum dose of prednisolone required to induce remission, and the

presence of other diseases. The outlook is worse in older patients and in patients with extensive disease.

**Patient Education.** Minimize trauma to the skin because the patient's skin is fragile both from the disease and from the use of topical and systemic steroids.The patient's understanding of the disease and education is important because of the chronic nature of this disorder.Educate patients regarding their medications. They should know about dose, adverse effects, and symptoms of toxicity so they can report adverse effects to the physician.Educate patients about appropriate wound care.

## 10.2. Pemphigus Erythematosus

**Synonyms and related keywords:** Senear-Usher syndrome, pemphigus seborrheic, lupus erythematosus, pemphigus foliaceus

**Background:** Pemphigus erythematosus, also known as Senear-Usher syndrome, is an overlap syndrome with features of lupus erythematosus (LE) and pemphigus foliaceus. Pemphigus is demonstrated by acantholysis and immunoglobulin deposits in the interkeratinocyte substance. The lupus component is demonstrated by circulating antinuclear antibodies (ANA) and sometimes by immunoglobulin and complement deposits at the dermoepidermal junction. The disease has a better prognosis than pemphigus foliaceus, but it can be chronic.

**Pathophysiology.**Patients present with vesiculobullae or superficially eroded lesions, which may ooze and crust, particularly in sun-exposed areas, such as the face, the upper part of the chest, and the back. Pemphigus may be photoactivated. LE is the classic autoimmune disease that demonstrates photosensitivity. It appears that a genetic predisposition to autoimmunity combines with a sensitivity to ultraviolet light leading to an overlap of these 2 diseases in rare cases.

**Causes.** Patients with pemphigus develop an autoimmune response directed against desmosomes. In patients with pemphigus foliaceus and its variant, pemphigus erythematosus, the target antigen is desmoglein 1. Desmogleins are desmosomal proteins important in keratinocyte adhesion. The binding of autoantibodies is postulated to result in a cascade of biochemical intracellular events that eventuates in the loss of desmosome function.Certain HLA haplotypes (A10 or A26, DRw6) are thought to be associated, suggesting a genetic predisposition.

**Frequency.** The incidence of pemphigus is 0.5-3.2 cases per 100,000 population per year. Patients with pemphigus erythematosus comprise only a small subgroup of those with pemphigus.

**Morbidity.**With timely diagnosis and treatment, the disease typically has a good prognosis. Some patients may ultimately develop symptoms classified as criteria for systemic lupus erythematosus (SLE) by the American Rheumatism Association (ARA).

**Race.**Pemphigus erythematosus, like other variants of pemphigus erythematosus and LE, may be increased in patients who express specific human leukocyte antigen (HLA) haplotypes. Those identified to have pemphigus erythematosus are positive for human leukocyte antigen A10 (HLA-A10) or human leukocyte antigen A26 (HLA-A26) and human leukocyte antigen DRW6 (HLA-DRW6).
**History.**Onset and progression are typically slow. Although the distribution of the lesions should suggest induction by sunlight, the patient may be completely unaware of the photosensitive nature of the disorder.
**Physical.**Lesions typically involve the scalp, the face, the upper part of the chest, and the back.Patients with pemphigus erythematosus classically present with small, flaccid bullae with scaling and crusting. Occasionally, the appearance may suggest a papulosquamous disorder.Secondary infection may occur, resulting in impetiginization, in healing with pigment changes, and in scarring.
On the face, pemphigus erythematosus presents on the bridge of the nose and on the malar areas as in the butterfly distribution seen in LE.With extensive involvement, patients may present with an exfoliative erythroderma.
The skin may be tender. Patients with pemphigus erythematosus do not typically develop mucous membrane involvement, which can be seen in some other variants of pemphigus.Electrolyte imbalance and loss of temperature control can occur with extensive skin involvement.
**Complications.**The types of medications used to control severe pemphigus erythematosus may lead to serious iatrogenic disorders.
**Lab Studies.** Direct immunofluorescence. Linear deposits of immunoglobulin G (IgG) and C3 are present in the intercellular space of the epidermis.Granular deposits of C3 and IgG at the dermoepidermal junction are present in 80% of patients, particularly in biopsy specimens from the face or other sun-exposed areas.
Immunoelectron microscopy: IgG and C3 deposits are localized to the epidermal cell membranes and the upper dermis.
Patients with pemphigus erythematosus may have other laboratory abnormalities suggestive of SLE; these include anemia, lymphopenia, thrombocytopenia, renal abnormalities, proteinuria, or a positive rheumatoid factor.
**Procedures.**Select an early vesicle or bulla for skin biopsy. Perilesional skin is tested on immunofluorescence studies.
**Histologic Findings.**Intraepidermal superficial bullae are usually within the granular layer or just below it. Acantholysis may occur in the blister floor or roof. Old lesions may have follicular hyperkeratosis with acantholysis and dyskeratosis.
**Medical Care.**Topical therapy - topical corticosteroids are useful for patients with limited diseases or as an adjunct to systemic therapy. Selection of the appropriate topical steroid strength and vehicle depends on the body site, the age of the patient, and the potential for steroid adverse effects. Use of daily sunscreen and sun protection is necessary.
Systemic therapy - systemic steroids have been the mainstay of therapy for widespread pemphigus since their first use in 1950. Prednisone 1-2 mg/kg/d as a

single morning dose or as intravenous pulses may control the disease. Appropriate monitoring and follow-up care to avoid steroid adverse effects is critical.
Dapsone is effective in some patients with pemphigus erythematosus. Patients tend to respond relatively quickly, with improvement within several weeks. It can be a steroid-sparing drug. The possible mode of action is stabilization of lysosomal membranes and inhibition of polymorphonuclear leukocyte (PMN) toxicity. The recommended dose is 100-200 mg/d. Hemolytic jaundice may result in people with G-6-PD deficiency. Other adverse effects include agranulocytosis, leading to death, headaches, malaise, hepatitis, hypersensitivity reactions, and neuropathy. Caution is required.
Azathioprine is a potent immunosuppressive agent that has been used as a steroid-sparing agent. The usual doses are 75-150 mg (2-3 mg/kg/d) combined with 40-80 mg of prednisone. After initial control of the disease is obtained, tapering to maintenance doses of azathioprine is recommended. Patients who are thiopurine methyltransferase activity deficient (11% of the population) are at an increased risk of bone marrow toxicity with this agent.
Other useful drugs include the following: tetracycline and niacinamide, cyclophosphamide, methotrexate, hydroxychloroquine, plasmapheresis, mycophenolate mofetil, extracorporeal photochemotherapy.
**Diet.**Patients on long-term glucocorticoids should increase their intake of calcium and vitamin D as well as bisphosphates in an effort to prevent osteoporosis.
**Activity.**Patients should use appropriate sun-smart behaviors and protective clothing to minimize sun exposure that may exacerbate disease activity. Sun avoidance and sun protection are recommended.
**Prognosis.**The prognosis of pemphigus erythematosus is better than that of pemphigus vulgaris. With good dermatologic care, patients with pemphigus erythematosus are often able to live normal lives.

## 10.3. Dermatitis Herpetiformis

**Background.**Dermatitis herpetiformis (DH) is an immune-mediated blistering skin disease with an associated, most often asymptomatic, gluten-sensitive enteropathy (GSE). Characteristic skin lesions found in patients with DH are extremely itchy grouped vesicles most frequently located on extensor surfaces. Skin lesions of DH can be treated with dapsone, with relief of symptoms within 24-48 hours of the start of therapy. Alternatively, many patients can control the skin disease with a gluten-free diet, often without medication. Both the skin and gastrointestinal systems are affected.
**History.**In 1884, Louis Duhring described DH as a skin disorder accompanied by severe itching and burning and characterized by herpetiform inflammatory papules and vesicles. The initial description also included patients with other blistering disease including pemphigoid. The presence of immunoglobulin A (IgA) deposits in the skin of patients with DH confirms the unique nature of the eruption. DH is

associated with GSE, and the skin disease can be controlled by strict adherence to a gluten-free diet.

Patients with DH and associated GSE have a granular pattern of IgA deposits, while those with a similar clinical eruption and linear IgA deposits do not have associated GSE, which confirms that patients with DH have characteristic clinical presentation, granular IgA deposits in the skin, and associated GSE.

**Causes.**The pathogenesis of DH is associated with the presence of GSE; an increased expression of human leukocyte A1 (HLA-A1), human leukocyte antigen B8 (HLA-B8), human leukocyte antigen DR3 (HLA-DR3), and human leukocyte antigen DQ2 (HLA-DQ2) haplotypes; and granular deposition of IgA at the dermal-epidermal junction of the skin.

***Gluten sensitivity.*** Patients with DH uniformly have associated GSE. GSE in patients with DH most often is asymptomatic. Fewer than 10% of patients have bloating, diarrhea, or symptomatic malabsorption.

***Mild steatorrhea or other signs of mild malabsorption***, such as altered D-xylose absorption or iron or folate deficiency, can be demonstrated in 20-30% of patients with DH. Patients with DH and no apparent gastrointestinal disease can be induced by increased gluten intake, which often is termed *latent GSE (celiac disease)*.

Gluten is a protein present in barley, rye, and wheat but not in rice. Oats generally are well tolerated in moderate amounts. Strict compliance with a gluten-free diet results in normalization of the small bowel mucosal changes and control of the cutaneous manifestations of DH in most patients.

The critical role of associated GSE in the pathogenesis of DH is confirmed by the fact that resumption of a gluten-containing diet in patients with DH results in the return of characteristic skin disease.

***Immunoglobulin A.***IgA deposits are found in a granular pattern at the dermal-epidermal junction in patients with DH. These deposits are present throughout the skin. IgA deposits in the skin contain both kappa and lambda light chains, indicating that they are polyclonal. Secretory component has not been demonstrated in the skin of patients with DH. The IgA-associated protein J chain has been found by some workers in cutaneous IgA, suggesting a mucosal origin, although this finding has not been documented by other laboratories. Deposits of the third component of complement, C3, also may be present in a similar pattern at the dermal-epidermal junction. The membrane attack complex, C5-C9, also has been identified in perilesional skin, although it may be inactive and not contribute to cell lysis. The mechanism whereby IgA binds to the skin of patients with DH is unknown. IgA deposits in DH skin have been shown to function in vitro as a ligand for neutrophil migration and binding in skin. Neutrophil accumulation in the skin of patients with DH is the characteristic histologic finding. Collagenase and stromelysin 1 may be induced in basal keratinocytes by cytokines released from neutrophils or by contact with keratin from damaged basement membrane matrix. Stromelysin 1 may contribute to blister formation. IgA deposits disappear after long-term avoidance of dietary gluten, which suggests that IgA plays a critical role in the development of skin lesions in patients with DH. Patients with bullous

pemphigoid, cicatricial pemphigoid, Henoch-Schönlein purpura, and alcoholic liver disease also may have IgA deposits in normal skin; however, the pattern of IgA deposits is different than that seen in patients with DH.

IgA-circulating immune complexes are present in 25-35% of patients with DH, although no association with disease severity has been noted. These immune complexes also have been noted in patients with isolated GSE and have been believed to be related to the presence of the gut disease. IgA antibodies to gliadin (a portion of wheat protein), reticulum, and smooth muscle endomysium also have been noted in patients with DH and those with isolated GSE. IgA endomysial antibodies are most specific for gluten sensitivity and are found in patients with DH and those with isolated GSE. The presence of IgA antiendomysial antibodies correlates with the extent of the gut disease, and some patients with DH do not have detectable IgA antiendomysial antibodies even in the presence of active skin disease. The criterion standard for the diagnosis of DH remains the presence of granular deposits of IgA in normal-appearing perilesional skin.

***Human leukocyte antigens.*** A genetic predisposition for DH has been established conclusively by HLA studies. Patients with DH have an increased expression of the HLA-A1, HLA-B8, HLA-DR3, and HLA-DQ2 haplotypes (see Table 10.1). This is identical to the HLA association found in patients with isolated GSE. Most persons with these HLA types do not have DH or GSE. The mechanism(s) by which HLA association results in the development of disease is unknown. In the presence of additional factors (including exposure to gluten), it is hypothesized that patients with genetic predisposition, as determined by HLA status, may develop a cell-mediated immune response resulting in T-cell activation, elaboration of cytokines, and tissue damage in the small bowel mucosa. The mechanism whereby this gut mucosal injury results in skin disease in patients with DH and not in those with isolated GSE is unknown.

**Table 10.1 Associations of Human Leukocyte Antigen and Dermatitis Herpetiformis**

| HLA | DH (%) | Control Population (%) |
|---|---|---|
| B8 | 58-87 | 20-30 |
| DR3 | 90-95 | 23 |
| DQ2 | 95-100 | 40 |

***Other associations.*** Associations of DH include gastrointestinal and autoimmune diseases (see Table 10.2). Celiac disease (gluten sensitivity in absence of DH) usually involves more severe and widespread intestinal involvement. An increased risk is seen of gastrointestinal lymphomas and non-Hodgkin lymphoma. Thyroid abnormalities include hypothyroidism, hyperthyroidism, thyroid nodules, and thyroid cancer. Gluten-free diet may reduce incidence of DH-associated lymphomas. Gastric manipulation (surgery) may induce DH. Several chemicals have been associated with induction of DH, including potassium iodide and cleaning solutions.

**Table 10.2 Diseases Associated with Dermatitis Herpetiformis**

| Autoimmune | Gastrointestinal | Neoplastic |
|---|---|---|
| Dermatomyositis | Gluten enteropathy | Gastrointestinal lymphoma |
| Insulin-dependent diabetes mellitus | Gastric atrophy | Non-Hodgkin lymphoma |
| Myasthenia gravis | Gastric hypochlorhydria | - |
| Rheumatoid arthritis | Pernicious anemia | - |
| Sjögren syndrome | - | - |
| Systemic lupus erythematosus | - | - |
| Thyroid abnormalities | - | - |

**Physical.**Flesh-colored–to–erythematous vesicles appear in a herpetiform pattern, symmetrically distributed over extensor surfaces including elbows, knees, buttocks, shoulders, and the posterior (nuchal) scalp.

Erythematous papules and urticaria-like plaques occur less frequently; bullae are rare.Patients often present with erosions and crusts in the absence of vesicles. Typical symptoms include burning, stinging, and intense pruritus. Patients often note stinging or burning of the skin before the appearance of new lesions.Rarely, if ever, are patients totally asymptomatic, although the degree of itching experienced by patients varies.Oral mucosa lesions occur infrequently in patients with DH. Palms and soles usually are spared. DH is a lifelong disease, although periods of exacerbation and remission frequently are seen.

**Complications.**Complications relate to the gluten-sensitive enteropathy, incidence of lymphoma, and potential adverse effects of medications (dapsone).

**Procedures.**Light microscopy features are not diagnostic of DH, and direct immunofluorescence is required to confirm the diagnosis.Biopsies for direct immunofluorescence should be performed on perilesional (normal-appearing) skin, since neutrophils may degrade the IgA in active lesions.

**Histologic Findings.**Biopsy specimens of lesional skin reveal neutrophils in the dermal papillae with fibrin deposition, neutrophil fragments, and edema. Eosinophils may be present. Papillary microabscesses form and progress to subepidermal vacuolization and vesicle formation. Vesicles form in the lamina lucida, the weakest portion of the dermal-epidermal junction.

Histologic differential diagnosis of early skin lesions includes bullous lupus erythematosus, bullous pemphigoid, epidermolysis bullosa acquisita, and linear IgA disease. Histologic differential diagnosis of late skin lesions includes bullous drug eruption, bullous pemphigoid, erythema multiforme, and herpes gestationis.

Granular IgA deposits in dermal papillae of perilesional skin observed by direct immunofluorescence is the criterion standard of diagnosis.

**Medical Care.**Dapsone (diaminodiphenyl sulfone) and sulfapyridine are the primary medications used to treat DH. For many years, rapid improvement on dapsone was a chief diagnostic criterion of the disease; however, many diseases respond to dapsone, and this should not be used as a diagnostic criterion. Dapsone

often is used initially; sulfapyridine is substituted in patients unable to tolerate dapsone. The mechanism for therapeutic effect of dapsone in DH is unclear. Improvement may be dramatic; symptomatic improvement of skin lesions often begins within hours. No new lesions form for up to 2 days after a dose of dapsone; however, dapsone does not improve gastrointestinal mucosal pathology.
Other, less effective, treatments for DH include colchicine, cyclosporine, and prednisone. Cyclosporine should be used with caution in patients with DH because of a potential increase in intestinal lymphoma.
NSAIDs may exacerbate DH; however, ibuprofen appears to be safe. Iodides may elicit or exacerbate DH.
**Consultations.**Consider consultation with a gastroenterologist for evaluation and recommendation regarding GSE.Consult with a dietitian regarding patients who are modifying dietary intake to avoid gluten or institute an elemental diet.
**Diet.** Most patients (as many as 80%) respond to gluten-free diet with control of their skin disease. Some patients are able to discontinue the use of dapsone totally. Compliance with a gluten-free diet requires a motivated patient, and the best treatment response occurs with absolute gluten restriction in the diet.Strict dietary vigilance may be required for 5-12 months before the dapsone dose can be reduced.Gluten-free diet is the only sustainable method of eliminating the disease, not only from the skin, but also from the gastrointestinal mucosa.Patients on a gluten-reduced diet may experience decrease of symptoms; therefore, diet reduces the dosage of dapsone required for disease control.Neither IgA deposition nor circulating antibodies correlate with gluten intake in short duration studies; however, some studies have suggested a correlation exists with complement deposition. Avoidance of dietary gluten for 10 years or more has resulted in loss of cutaneous IgA deposits that return upon reinstitution of gluten in the diet.Elemental diets may improve the disease within weeks. These diets consist of free amino acids, small amounts of triglycerides, and short chain polysaccharides; they are marketed by pharmaceutical companies. One report has suggested that this improvement may be independent of gluten ingestion; however, this finding has not been confirmed.
**Prognosis.** DH is an ongoing disease process with variability of severity.Prognosis is good for patients who can tolerate dapsone and the few that maintain a gluten-free diet (in whom the incidence of associated lymphoma may be less).

## 10.4. Bullous Pemphigoid

**Background.**Bullous pemphigoid (BP) is a chronic, autoimmune, subepidermal, blistering skin disease that rarely involves mucous membranes. BP is characterized by the presence of immunoglobulin G (IgG) autoantibodies specific for the hemidesmosomal BP antigens BP230 (BPAg1) and BP180 (BPAg2).
**Pathophysiology.**IgG autoantibodies bind to the skin basement membrane in patients with BP. The binding of antibodies at the basement membrane activates complement and inflammatory mediators. Activation of the complement system is

thought to play a critical role in attracting inflammatory cells to the basement membrane. These inflammatory cells are postulated to release proteases, which degrade hemidesmosomal proteins and lead to blister formation. Eosinophils are characteristically present in human patients' blisters as demonstrated by histopathologic analysis, although their presence is not an absolute diagnostic criterion.

The precise role of BP antigens in the pathogenesis of BP is not clear. BPAg1 (BP230) is an intracellular component of the hemidesmosome; BPAg2 (BP180, type XVII collagen) is a transmembranous protein with a collagenous extracellular domain. Passive transfer experiments in newborn mice have demonstrated that rabbit antibodies against mouse BPAg2 can induce subepidermal blisters similar to those observed in patients with BP. Furthermore, anti-BP180 NC16A domain autoantibodies purified from patients with BP are capable of inducing dermal-epidermal separation in cryosections of normal human skin.

Serum levels of autoantibodies against BPAg2 are reportedly correlated with disease activity in some studies. Induction of antibodies against BPAg1 in rabbits does not induce primary blistering, but it can enhance the inflammatory response at the basement membrane. The role of autoantibodies specific for BP antigens in the initiation and the perpetuation of disease is unknown.

Currently, no active experimental model is available to dissect the induction phase of the disease. Nevertheless, the autoantibody response can be induced in healthy BALB/c mice by immunizing the mice with synthetic peptides of the mouse type XVII collagen NC16A domain, the target region of autoantibodies in human patients affected with BP.

Eotaxin, an eosinophil-selective chemokine, is strongly expressed in the basal layer of the epidermis of lesional BP skin and parallels the accumulation of eosinophils in the skin basement membrane zone area. It may play a role in the recruitment of eosinophils to the skin basement membrane area.

**Causes.**The cause of BP is not known; however, several potentially relevant factors have been identified.

***Immunogenetics.*** Immunogenetic analyses have identified that the human leukocyte antigen (HLA) haplotype, DQB1*0301, is increased in patients with BP. In one study, peripheral blood lymphocytes from patients with BP who are positive for HLA-DQB1*0301 proliferated in the presence of the BP180 antigen. In these studies, the ability of the patient's T cells to respond to the target BP antigen was restricted by the HLA haplotype. This HLA haplotype is postulated to be important in the presentation of the target antigen by antigen-presenting cells in the initial development of the autoimmune response.

***Age.*** BP is most common in patients in their fifth to seventh decades of life. Investigators have postulated that intrinsic changes in the immune system with aging may be a factor in the initiation of an autoimmune response against BP antigens.Alternately, repeated trauma to the skin may lead to the development of an immune response against normal skin proteins.

***Epitope spreading.*** The autoimmune reaction may extend by an immunologic phenomenon termed epitope spreading, whereby a relatively restricted immune response spreads to involve different sites on the same autoantigen and to involve different autoantigens.This phenomenon has been well documented in animal models of autoimmune diseases. Epitope spreading may explain the presence of an immune response against 2 target antigens (BPAg1 and BPAg2) as well as multiple epitopes on the target antigens.

***Complement activation.*** BP autoantibodies bind to the hemidesmosome/upper lamina lucida areas of the skin basement membrane. Complement activation follows this binding as detected by direct immunofluorescence (DIF) studies that demonstrate in situ deposition of complement components (typically C3) at the basement membrane in patients with BP.Complement activation leads to the recruitment of inflammatory cells to the basement membrane zone. The enzymes released by these inflammatory cells cleave BPAg2 in vitro and are postulated to be important in blister formation.

***Chemokines.*** The histologic hallmark for BP is the prominent eosinophil infiltration at the skin basement membrane area. Eosinophil migration and activation is likely induced by chemokines.The expression of eotaxin, a chemokine associated with eosinophil migration, is increased in the epidermis of BP lesions. Similarly, eotaxin expression is increased on endothelial cells in biopsy samples obtained from the skin of patients with BP. This increased epidermal and endothelial expression of eotaxin may be important in the recruitment of eosinophils to the basement membrane in patients with BP.At the skin basement membrane, eosinophils can release proteolytic enzyme 92-kD gelatinase, which cleaves BPAg2 in vitro.Interleukin 5, an interleukin with eosinophil chemoattractant and activation properties, has also been found in the skin of patients with BP. It may play a role in eosinophil recruitment to the skin.

**Frequency.**BP is uncommon, and its frequency is unknown. Internationally:BP has been reported to occur throughout the world. In France and Germany, the reported incidence is 6.6 cases per million people per year. In Europe, BP was identified as the most common subepidermal autoimmune blistering disease.

**Mortality/Morbidity.**BP is a chronic inflammatory disease. If untreated, the disease can persist for months or years, with periods of spontaneous remissions and exacerbations. In most patients who are treated, BP remits within 1.5-5 years. Patients with aggressive or widespread disease, those requiring high doses of corticosteroids and immunosuppressive agents, and those with underlying medical problems have increased morbidity and risk of death. Because the average age at onset of BP is about 65 years, patients with BP frequently have other comorbid conditions that are common in elderly persons, thus making them more vulnerable to the adverse effects of corticosteroids and immunosuppressive agents.

BP may be fatal, particularly in patients who are debilitated. The proximal causes of death are infection with sepsis and adverse events associated with treatment. Patients receiving high-dose corticosteroids and immunosuppressants are at risk for peptic ulcer disease, GI bleeds, agranulocytosis, and diabetes.

BP involves the mucosa in 10-25% of patients. Patients who are affected may have limited oral intake secondary to dysphagia. Erosions secondary to rupture of the blisters may be painful and may limit patients' daily living activities. Blistering on the palms and the soles can severely interfere with patients' daily functions. BP lesions typically heal without scarring or milia formation.

**Age.** BP primarily affects elderly individuals in the fifth through seventh decades of life, with an average age at onset of 65 years. BP of childhood onset has been reported in the literature.

**History.**The onset of BP may be either subacute or acute, with widespread, tense blisters. Significant pruritus is frequently present. In some patients, the blisters arise after persistent urticarial lesions. BP has been reported following several non-bullous, chronic, inflammatory skin diseases, such as lichen planus and psoriasis.BP has been reported to be precipitated by ultraviolet irradiation, x-ray therapy, and exposure to some drugs.Drugs associated with BP include furosemide, ibuprofen and other non-steroidal anti-inflammatory agents, captopril, penicillamine, and antibiotics.BP has been reported to develop shortly after vaccination, particularly in children.

**Physical.**BP may present with several distinct clinical presentations, as follows: generalized bullous, vesicular, vegetative, generalized erythroderma, urticarial, and nodular variants.

***Generalized bullous form.*** The generalized bullous form is the most common presentation.Tense bullae arise on any part of the skin surface, with a predilection on the flexural areas of the skin. Oral and ocular mucosa involvement rarely occurs and, when seen, is of minor clinical significance.The bullae can occur on normal-appearing, as well as erythematous, skin surfaces.The bullae usually heal without scarring or milia formation.

***Vesicular form.*** The vesicular form is less common.It manifests as groups of small, tense blisters, often on a urticarial or erythematous base.

***Vegetative form.*** The vegetative form is very uncommon, with vegetating plaques in intertriginous areas of the skin, such as the axillae, the neck, the groin, and inframammary areas.This form of BP closely resembles pemphigus vegetans.

***Generalized erythroderma form.*** This rare presentation can resemble psoriasis, generalized atopic dermatitis, or other skin conditions characterized by an exfoliative erythroderma.Patients with this variant may develop vesicles or bullae.

***Urticarial form.*** Some patients with BP initially present with persistent urticarial lesions that subsequently convert to bullous eruptions.In some patients, urticarial lesions are the sole manifestations of the disease.

***Nodular form***. This rare form, termed pemphigoid nodularis, has clinical features that resemble prurigo nodularis, with blisters arising on normal-appearing or nodular lesional skin.

***Acral form***. In childhood-onset BP associated with vaccination, the bullous lesions predominantly affect the palms, the soles, and the face.

**Complications.** Secondary infection may occur because of the presence of multiple erosions and immunosuppressants used to control the disease. These

infections may be either systemic or localized to the skin. Cutaneous infection increases the risk of scarring and delays wound healing.Malignancies due to immunosuppressants have been reported. Case-control series in patients with BP have failed to detect an increased incidence of malignancy in patients with BP when compared with age- and sex-matched controls. Bone marrow suppression may occur in patients receiving immunosuppressants.Growth retardation may occur in children receiving systemic corticosteroids and immunosuppressants. Adrenal insufficiency may occur following prolonged use of glucocorticoids. Osteoporosis and bone fractures may result following the use of systemic corticosteroids.

**Lab Studies.** To establish a diagnosis of PB, the following tests should be performed: histopathologic analysis from the edge of a blister and DIF studies on normal-appearing perilesional skin. If the DIF result is positive, indirect immunofluorescence (IDIF) is performed using the patient's serum. The preferred substrate for IDIF is salt-split normal human skin substrate.

***Direct immunofluorescence studies.*** DIF studies demonstrate in vivo deposits of antibodies and other immunoreactants, such as complement. DIF tests usually demonstrate IgG (70-90% of patients) and complement C3 deposition (90-100% of patients) in a linear band at the dermal-epidermal junction. This pattern of immunoreactants is not specific for BP and may be seen in cicatricial pemphigoid and epidermolysis bullosa acquisita. BP can be differentiated from these conditions by incubating the patient's skin biopsy sample in 1 mol/L salt prior to performing the DIF technique. This process induces cleavage through the lamina lucida. DIF on salt-split skin reveals IgG on the blister roof (epidermal side of split skin) in patients with BP, while, in CP and EBA, the IgG localizes to the blister floor (dermal side of split skin).The optimal location for DIF testing is normal-appearing perilesional skin. False-positive results can be observed when it is performed on lesional skin. Rarely, skin biopsy samples placed in transport media may yield false-negative results. This observation makes the use of fresh tissue the preferred substrate for DIF studies.

***Indirect immunofluorescence.*** IDIF studies document the presence of IgG circulating autoantibodies in the patient's serum that target the skin basement membrane component. Seventy percent of patients with BP have circulating autoantibodies that bind to split skin. The titer of circulating antibody is not correlated with the disease course.IDIF studies can be used to detect the patient's IgG circulating autoantibodies that bind to the epidermal roof (upper part) of the salt-split skin substrate.

**Other Tests.**Experimental procedures available in research laboratories include direct and indirect immunoelectron microscopy, immunoblotting, immunoprecipitation, and enzyme-linked immunosorbent assay (ELISA).

***Direct and indirect immunoelectron microscopy.*** Direct and indirect immunoelectron microscopy (immunoEM) ultrastructurally localize in vivo–bound IgG autoantibodies (direct immunoEM) or the binding site of circulating IgG autoantibodies (indirect immunoEM) at the basement membrane.IgG

autoantibodies are detected at the hemidesmosome/upper lamina lucida areas of the skin basement membrane.

***Immunoblotting.*** Immunoblotting or Western blotting demonstrates reactivity of IgG in the sera of patients with proteins extracted from healthy human skin.The sensitivity of immunoblotting varies. In 75% of patients, a reaction occurs with the BP230 antigen, while, in 50% of patients, a reaction occurs with the BP180 antigen.

***Immunoprecipitation.*** Like immunoblotting, immunoprecipitation demonstrates reactivity with BP230 and BP180. Unlike immunoblotting, immunoprecipitation is performed with native, rather than denatured, protein and is more sensitive. Immunoprecipitation is more difficult to perform and generally less available than immunoblotting.In most cases, immunoprecipitation detects autoantibodies specific for BP230 and BP180.

***Enzyme-linked immunosorbent assay.*** The ELISA technique analyzes the BP antigen-specific IgG autoantibodies in the patients' sera by using various lengths of recombinant proteins of the BPAg1 or BPAg2 antigens. In several reports, ELISA has been demonstrated to be highly sensitive and specific, but it remains experimental at the present time.ELISAs based on recombinant proteins encoded by BP230 and BP180 have been developed. These assays are not commercially available, but they offer promise as investigational tools. An ELISA based on BP180 demonstrates sera reactivity with more than 90% of patients with BP.

**Histologic Findings.**The histopathologic examination demonstrates a subepidermal blister. The inflammatory infiltrate is typically polymorphous, with an eosinophil predominance. Mast cells and basophils may be prominent early in the disease course. Lesional skin biopsy specimens may reveal a predominantly neutrophilic infiltrate or minimal inflammation.

**Medical Care.** As in other autoimmune bullous diseases, the goal of therapy is to decrease blister formation, to promote healing of blisters and erosions, and to determine the minimal dose of medication necessary to control the disease process. Therapy must be individualized for each patient, keeping in mind preexisting conditions and other patient-specific factors.

Treatment is directed at reducing the inflammatory response and autoantibody production. Although target-specific therapy is the "Holy Grail" for immunodermatologists, non–target-specific treatments are currently used. The most commonly used medications are anti-inflammatory agents (e.g. corticosteroids, tetracyclines, dapsone) and immunosuppressants (e.g. azathioprine, methotrexate, mycophenolate mofetil, cyclophosphamide). A recent article from Europe provided evidence that strong topical corticosteroid treatment may achieve disease control while avoiding systemic adverse effects from systemic corticosteroids.

**Consultations.**Treatment of patients with BP requires coordination of care between the dermatologist and the patient's primary care provider. Patients with oral disease may require an otolaryngologist and/or a dentist for evaluation and

care.An ophthalmologist should evaluate patients with suspected ocular involvement and those requiring prolonged high-dose steroids.

**Diet.** The lesions may flare in patients with oral disease after eating hard and crunchy foods, such as chips, raw fruits, and vegetables.For patients treated with systemic corticosteroid for longer than 1 month, a combined supplement of calcium and vitamin D should be instituted to prevent osteoporosis.

**Prognosis.** Most patients affected with BP require therapy for 6-60 months, after which many patients experience long-term remission of the disease. However, some patients have long-standing disease requiring treatment for years.Most mortality associated with BP occurs secondary to the effects of the medications.The population at risk for BP is at an increased risk for comorbid conditions, such as hypertension, diabetes mellitus, and heart diseases, which treatment may exacerbate.

**Patient Education.** Patients should avoid trauma to the skin. Patients' skin is fragile from the disease, as well as from the use of topical and systemic steroids.Patients should be educated about their disease and treatments, so that they can report adverse effects to their physicians.

**Special Concerns.** Elderly patients with BP who have other significant health problems, such as diabetes mellitus, hypertension, or heart disease, may require treatment with a more conservative approach, using topical corticosteroids (clobetasol), tetracyclines, and/or low doses of systemic corticosteroids (prednisone 10-20 mg/d). In all patients, the goal of treatment is to achieve disease control with minimal symptoms and adverse effects from treatment.

# XI. MYCOBACTERIAL INFECTIONS

## 11.1. Leprosy

**Synonyms and related keywords:** Hansen's disease, Hansen disease, indeterminate leprosy, tuberculoid leprosy, borderline tuberculoid leprosy, borderline borderline leprosy, borderline lepromatous leprosy, lepromatous leprosy

**Background.**Leprosy is a chronic granulomatous disease, caused by *Mycobacterium leprae,* which affects principally the skin and peripheral nervous system.

The earliest description of leprosy comes from India around 600 BC. It was then described in the Far East around 400 BC. In the fourth century, the disease was imported into Europe, where it peaked in incidence in the 13th century. The disease has now nearly disappeared from Europe. Affected immigrants spread leprosy to North America.

Leprosy, also known as Hansen's disease, is a chronic infectious disease that primarily affects the skin, the peripheral nerves, the upper respiratory tract, and the eyes. The causative agent is an acid-fast bacterium, *Mycobacterium leprae*, first identified in 1873 by the Norwegian physician, Gerhard Henrik Armauer Hansen.

Leprosy was considered a divine curse for sin in the Old Testament and karma in Buddhism. The term leprosy originates from the Latin word *lepros*, meaning defilement. The fact that leprosy has been deemed an incurable disease, causing severe deformities and disabilities, has resulted in severe stigmatization. This has resulted in double suffering by victims, both from the disease itself and from public discrimination. Although documented since antiquity, leprosy currently remains endemic in some developing parts of the world.

Armauer Hansen discovered *M. leprae* in Norway in 1873. It was the first bacillus to be associated with human disease. Despite this discovery, leprosy was not initially thought to be an infectious disease.

Animal reservoirs of leprosy have been found in 3 species: 9-banded armadillos, chimpanzees, and mangabey monkeys.

**Pathophysiology.**The areas most commonly affected by leprosy are the superficial peripheral nerves, skin, mucous membranes of the upper respiratory tract, anterior chamber of the eyes, and testes. These areas tend to be cooler parts of the body. Tissue damage is caused by the degree to which cell-mediated immunity is expressed, the extent of bacillary spread and multiplication, the appearance of tissue-damaging immunologic complications (i.e. lepra reactions), and the development of nerve damage and its sequelae. *M. leprae* is an obligate intracellular acid-fast bacillus with a unique ability to enter nerves.

**Causes.**Leprosy is caused by *M. leprae,* an acid-fast bacillus. Only the lepromatous form is thought to be infectious.Exposure to the nasal discharge of those that remain untreated for years is thought to be the main cause of infection.Most persons are immune to leprosy. Subclinical disease is common in

endemic areas, and the infection progresses to clinical disease in only a select few.Transmission is not completely understood. In addition to exposure respiratory secretions, exposure to insect vectors and infected soil has been suspected as a possible mode of transmission. Household contacts of patients are at little risk of acquiring the disease.

**Frequency.**The worldwide prevalence of leprosy is reported to be 5.5 million cases. The majority of affected persons live in the tropics and subtropics. Worldwide, 80% of the cases are found in 5 countries: India, Myanmar, Indonesia, Brazil, and Nigeria.

**Mortality/Morbidity.**If severe and left untreated, leprosy can cause significant debilitating deformity. Since 1943, when sulfone was introduced as the first effective treatment for leprosy, antibiotic treatment has dramatically improved patients' outcomes. Early diagnosis and effective antimicrobial treatment can arrest and even cure the disease.

**Race.**Leprosy occurs in all races. African blacks report a higher incidence of the tuberculoid form of leprosy. People with light skin and Chinese individuals have a greater tendency to have the lepromatous type of leprosy. Leprosy is endemic in Asia, Africa, the Pacific basin, and Latin America (excluding Chile). It is more a rural disease than urban disease.

**Sex.**In adults, the lepromatous type of leprosy is more common in men than women, with a male-to-female ratio of 2:1. In children, the tuberculoid form predominates, and no sex preference exists.

**Age.**Leprosy has a bimodal age distribution, with peaks in those aged 10-14 and in those aged 35-44 years. The disease is rare in infants. Children appear to be more susceptible to disease and tend to have the tuberculoid form.

The incubation period ranges from 6 months to 40 years or longer. The average incubation period is 2-3 years.

**History.**Several forms of leprosy range from the mildest indeterminate form to the most severe lepromatous type. Symptoms and physical findings vary depending on the stage of disease.

The disease is usually diagnosed on the basis of the following characteristic findings: anesthesia of a skin lesion or in the distribution of a peripheral nerve, thickened nerves, and typical skin lesions.

Prodromal symptoms are generally so slight that the disease is not recognized until a cutaneous eruption is present. Actually, 90% of patient present with numbness first, sometimes years before the skin lesions appear.

Temperature is the first sensation that is lost. Patients cannot sense extremes of hot or cold. The next sensation lost is light touch, then pain, and finally deep pressure. These losses are especially apparent in the hands and feet. A hypopigmented macule is often the first cutaneous lesion. From this stage, most lesions evolve into the lepromatous, tuberculoid or borderline types.

**Physical.*Indeterminate leprosy*** (IL). This early form causes one to a few hypopigmented, or sometimes erythematous, macules. Sensory loss is unusual.Most cases evolve from this state into one of the other forms, depending

on the patient's immunity to the disease. Those with strong immunity may become cured of disease. In some, the disease may persist in this indeterminate form. In those with weaker immunity, the disease progresses to one of the other forms.

***Tuberculoid leprosy*** (TT). Skin lesions are few in number. Usually, one erythematous large plaque is present, with well-defined borders that are elevated and slope down into an atrophic center. The lesions can become arciform or annular, and they can be found on the face, limbs or elsewhere, but spare intertriginous areas and the scalp.Another presentation involves a large asymmetric hypopigmented macule.Both types of lesions are anesthetic and involve alopecia. Spontaneous resolution can occur in a few years, leaving pigmentary disturbances or scars. Progression can also occur, leading to borderline-type leprosy. In rare instances in which a patient is untreated for many years, the lepromatous type can develop.Neural involvement is common in TT; it leads to tender, thickened nerves with subsequent loss of function. The great auricular nerve and superficial peroneal nerves are often prominent.

***Borderline tuberculoid leprosy*** (BT). Lesions in this form are similar to those in the tuberculoid form, but they are smaller and more numerous. The nerves are less enlarged, and less alopecia is present.Disease can remain in this stage, convert back to the tuberculoid form, or progress.

***Borderline borderline leprosy*** (BB). Cutaneous lesions consist of numerous, red, irregularly shaped plaques that are less well defined than those in the tuberculoid type. Their distribution may mimic those of the lepromatous type, but they are more asymmetric. Anesthesia is only moderate. Regional adenopathy may be present. Disease may remain in this stage, improve or worsen.

***Borderline lepromatous leprosy*** (BL). Lesions are numerous and consist of macules, papules, plaques, and nodules. Annular punched-out-appearing lesions that look like inverted saucers are common. Anesthesia is often absent. As with the other forms of borderline leprosy, the disease may remain in this stage, improve, or regress.

***Lepromatous leprosy*** (LL). Early cutaneous lesions consist mainly of pale macules. Later, infiltrations are present, with numerous bacilli. Macular lesions are small, diffuse, and symmetric. The skin texture does not change, and little or no loss of sensation occurs. The nerves are not thickened, and sweating is normal. The lateral eyebrows are affected by alopecia (i.e. madarosis), which spreads to the eyelashes and then the trunk. Scalp hair remains intact. Lepromatous infiltrations can be diffuse, nodules (called lepromas), or plaques. The diffuse type results in the appearance of a leonine facies. Neuritic lesions are symmetric and slow to develop. Eye involvement occurs, causing pain, photophobia, decreased visual acuity, glaucoma, and blindness. Testicular atrophy results in sterility and gynecomastia. Lymphadenopathy and hepatomegaly can result from organ infiltration. Stridor and hoarseness are a result of laryngeal involvement. Nasal infiltration can cause a saddle-nose deformity. Aseptic necrosis and osteomyelitis can occur with repeated trauma after joint invasion. Brawny edema of the lower extremities is a late finding.

**Complications.**Reactional states are the most common complications. These states can result in permanent neurologic sequelae, resulting in disability and deformity.Lepra type I reactions usually affect patients with borderline disease. A downgrading reaction represents a shift toward the lepromatous pole before the initiation of therapy. Reversal reactions are shifts toward the tuberculoid pole after the initiation of therapy.Lepra type II reactions, or ENL, is an immune complex–mediated reaction that occurs in patients with the BL or LL forms. The most common presenting symptoms are crops of painful erythematous nodules of the skin and subcutaneous tissue. The reaction usually manifests after a few years of therapy and resolves spontaneously after about 5 years. Associated fever, malaise, joint pain, nerve pain, iridocyclitis, dactylitis, and orchitis may be present.A Lucio phenomenon is an unusual type II reaction that is sometimes designated a type II reaction. It common in Mexico and Central America and is characterized by cutaneous hemorrhagic infarcts in patients with diffuse LL. Injuries can result in ulcerations, cellulitis, scarring, and bony destruction. Contractures can develop and result in fixation. Eye damage can result in lagophthalmos, ectropion, and entropion.

**Lab Studies.*Tissue smear testing.*** An incision is made in the skin, and the scalpel blade is used to obtain fluid from a lesion. The fluid is placed on a glass slide and stained by using the Ziehl-Neelson acid-fast method to look for organisms.The bacterial index (BI) is then determined.

***Histamine testing.*** This test is used to diagnose postganglionic nerve injury.Histamine diphosphate is dropped on normal skin and affected skin, and a pinprick is made through each site. The site forms wheal on normal skin but not where nerve damage exists.

***Methacholine sweat testing.*** This demonstrates the absence of sweating in leprous lesions.It is useful in dark-skinned patients in whom the flare with the histamine test cannot be seen.

***Skin biopsy.*** The skin biopsy sample should be examined for morphologic features and the presence of acid-fast bacilli.Biopsy is useful for determining the morphologic index (MI), which is used in the evaluation and treatment of patients. It is the number of viable bacilli per 100 bacilli in the leprous tissue.

***Sensory testing.*** Tactile and temperature sensations should be tested.A wisp of cotton can be used to test for anesthesia of the lesions.

***Lepromin testing.*** This test indicates host resistance to *M. leprae.* It results do not confirm the diagnosis, but they are useful in determining the type of leprosy. A positive finding indicates cell-mediated immunity, which is observed in TT. A negative finding suggests a lack of resistance to disease and is observed in LL. A negative result indicates a poorer prognosis. To perform this test, bacillary suspension is injected into the forearm. When the reaction is assessed at 48 hours, it is called the Fernandez reaction and indicates delayed hypersensitivity to antigens of *M. leprae* or mycobacterium that cross react. When the reaction is read at 3-4 weeks, it is called the Mitsuda reaction and indicates that the immune system is capable of mounting an efficient cell-mediated response.

**Polymerase chain reaction (PCR) analysis.** PCR can be used to detect and identify *M. leprae.*The technique is used most often when acid-fast bacilli are detected but clinical or histopathologic features are atypical. It is not useful when acid-fast bacilli are not detectable by means of light microscopy.

**Histologic Findings.**In the TT form, well-developed epithelioid granulomas are observed in the papillary dermis, often around neurovascular structures. The granulomas are surrounded by lymphocytes, which extend into the epidermis. Langhans giant cells are common. Dermal nerves are destroyed or swollen because of the granulomas. Acid-fast bacilli are not observed.

In the LL form, a diffuse infiltrate of foamy macrophages is present in the dermis below a subepidermal zone of uninvolved papillary dermis (i.e. grenz zone). An enormous number of acid-fast bacilli develop within the foamy macrophages, singly or in clumps called globi. Lymphocytes are scant, and giant cells are typically absent. Numerous bacilli invade the nerves, but these are fairly well preserved with little infiltrate. Nodular, or dermatofibroma-like lesions in LL, referred to as histoid leprosy, result in a diffuse fascicular arrangement of spindled cells in the dermis admixed with foamy macrophages that contain numerous bacilli.

In the BT form, well-developed epithelioid cell granulomas are apparent and diffuse, but few or no Langhans giant cells are observed. Few lymphocytes are present in the epidermis in this form, compared with the TT form. Bacilli are absent or rare, but they can be found in dermal nerves as well as in the arrector pilorum. Nerves are moderately swollen.

In the BB form, diffuse epithelioid granulomas that lack giant cells are observed in the dermis below the subepidermal grenz zone. Nerves are slightly swollen, and acid-fast bacilli are present in moderate numbers.

In the BL form, smaller granulomas with some foamy changes and numerous lymphocytes are observed. Nerves often have an onion-skin appearance due to invasion of the perineurium. A few epithelioid cells may be observed.

In the IL form, findings are nonspecific. Histiocytes and lymphocytes are scattered, with some concentration around dermal appendages and nerves. At times, an acid-fast bacillus can be observed in a nerve bundle. The number of dermal mast cells may be increased.

**Medical Care.**The management of leprosy includes chemotherapy to stop the infection; treatment to minimize potential physical deformities; and physical, social, and psychological rehabilitation. Potential deformities can be prevented by educating patients about how to deal with existing nerve damage and by treating any sequelae of this damage. Close follow-up is important to ensure patient compliance. Monitor for drug resistance and adverse reactions to medications.

The first-line drugs are dapsone, rifampin, and clofazimine. Other antibiotics include minocycline, ofloxacin, and clarithromycin.

Eyes, nerves, and the nose should be examined at follow-up to ensure the timely recognition of reactive disease.The real challenge in managing leprosy is the treatment of reactional states. Systemic steroids are effective in reducing

inflammation and edema in reversal reactions; thus, they are the most helpful medications in preventing nerve damage.Prednisone should be given at a dose of 40-80 mg/d for 5-7 days and then tapered slowly over 3-6 months. This long course is necessary to decrease the severity of disabilities and deformities.
Clofazimine can also be used as a steroid-sparing agent for reversal reactions.
Thalidomide is ineffective for the treatment of reversal reactions, but it is highly effective with erythema nodosum leprosum (ENL).
The goals of pharmacotherapy are to reduce morbidity, prevent complications, and eradicate the disease.
For drug treatment purposes, infections are classified as paucibacillary or multibacillary. Paucibacillary disease can be treated with a combination of 2 drugs, whereas multibacillary disease requires triple-drug therapy. The length of treatment depends on the type of disease and the access to medicine. The recommendations of the World Health Organization (WHO) and those in the United States are both mentioned here. *Corticosteroids*-- These are important anti-inflammatory agents used in the treatment of reactional leprosy. Corticosteroids are the reliable only in the treatment of reversal reactions. These medications can be used to treat leprosy reactions when a risk of neurologic deficits exists or when lesions occur in cosmetically important places. They can also be used to treat ENL.
**Surgical Care.** Emergency surgery may be necessary if a patient with profound nerve inflammation presents with a nerve abscess or loss of nerve function secondary to compression.Prompt recognition and surgical drainage of the abscess can often restore nerve function.Elective surgery may be required for correction of lagophthalmos (i.e. inability to close the eye).Reconstructive surgery can be used to repair nasal collapse in LL. Other surgery may be needed to improve function or for cosmesis. Contractures can be surgically repaired.
**Consultations.**Consultations with an ophthalmologist, plastic surgeon, orthopedic surgeon, otolaryngologist, neurosurgeon, and/or neurologist may be necessary. Reasons for a consultation with an ophthalmologist consult include the following: lagophthalmos, ENL-induced iritis, direct invasion of the anterior chamber of the eye by *M. leprae*, corneal and conjunctival insensitivity, infection or scarring from fifth and seventh cranial nerve involvement.
Rehabilitation medicine, including physical and occupational therapy, can help reduce morbidity.Consultation with a prosthetics specialist may also be appropriate.
**Activity.**Restrictions on activity depend on the extent of nerve damage. In patients with bone or joint destruction, weight bearing should be minimized. Patients with anesthesia of limbs need to be educated about their condition, and they should wear appropriate footwear.Plantar ulceration requires rest and avoidance of weight bearing. Weakness or paralysis requires physical therapy to prevent contractures.
**Further Outpatient Care.** WHO recommends 2 years of follow-up for paucibacillary disease and 5 years of follow-up for multibacillary disease. Patients should be monitored for possible lepra reactions.In some regions of the world, self-administration of medications is difficult. Medical posts or mobile units can be set

up for the administration of medications and management of health-related issues. Supervision may be required to achieve the maximum benefit from therapy.In patients taking dapsone, the complete blood count should be checked at frequent intervals early during the therapy and at less frequent intervals later during therapy. Sensation and muscle strength in the hands, feet, and eyes should be checked on a regular basis.

**Prevention.**Household contacts of patients with lepromatous disease should be annually monitored for 5 years after diagnosis. Children especially should be observed for the development of disease. Dapsone prophylaxis is no longer advocated.Attempts have been made to develop a vaccine against leprosy. The bacille Calmette-Guerin (BCG) vaccine has variable results in protection.

**Prognosis.**The prognosis depends on the stage of disease. In borderline cases, the disease has the potential to be down-graded to LL; these patients may have nerve damage.Even with corticosteroid treatment, neuritis may not be curable. The prognosis also depends on the patient's access to therapy, the patient's compliance, and the early initiation of treatment.

**Patient Education.**Patients first need an explanation of the diagnosis and prognosis. Their fears should be addressed because of the cultural stigma associated with leprosy.They may need psychological counseling because they may have difficulty in coming to terms with the disease or in feeling rejected by society.Patients need education on how to deal with anesthesia of a hand or foot. They must learn to carefully inspect their extremities for trauma and should be told to wear proper footwear.Inspecting limbs and eyes for onset of anesthesia or weakness is also important.Physical therapy and occupational therapy are important tools in rehabilitation.Patients need to learn how to recognize the onset of lepra reactions, and they should be told to seek immediate medical attention if these develop.Potential deformities can be prevented by educating patients about how to deal with existing nerve damage and by treating any sequelae of this damage.

**Medical/Legal Pitfalls.**Leprosy is a contagious transmissible disease, and cases should be reported to health officials when they are diagnosed.Discrimination against patients with leprosy in vocational matters is illegal.

**Special Concerns.**Pregnant women have decreased cell-mediated immunity and thus have an increased risk of acquiring the infection.If the disease is incubating, pregnancy can result in overt expression. They also have an increased incidence of type I and II lepra reactions. These events are most likely to occur in the third trimester.Congenital disease is rare, but infants born to mothers with leprosy have slow growth and a decreased birth weight. They have a high risk of contracting disease if the mother has LL.

## 11.2. Cutaneous Tuberculosis

**Synonyms and related keywords:**tuberculosis verrucosa cutis, miliary tuberculosis of the skin, scrofuloderma, tuberculous gumma, tuberculosis cutis orificialis, lupus vulgaris, erythema induratum, papulonecrotic tuberculid, lichen scrofulosorum, cutaneous TB

**Background.***Mycobacterium tuberculosis* is the causative agent of tuberculosis (TB) and a member of a group of closely related organisms in the *M. tuberculosis* complex: *Mycobacterium africanum, Mycobacterium bovis, Mycobacterium microti*, and *M. tuberculosis*. In 1882, Robert Koch discovered and isolated the tubercle bacillus (*M. tuberculosis*).

TB is an ancient disease. Signs of skeletal TB (Pott disease) were evident in Europe from Neolithic times (8000 BCE), in ancient Egypt (1000 BCE), and in the pre-Columbian New World. TB was recognized as a contagious disease by the time of Hippocrates (400 BCE), when it was termed "phthisis" (Greek from *phthinein*, to waste away).

World incidence of TB increased with population density and urban development so that by the Industrial Revolution in Europe (1750), it was responsible for more than 25% of adult deaths. Indeed, in the early 20th century, TB was the leading cause of death in the US. Neil Finsen won the Nobel Prize in Medicine in 1903 for introducing UV light into the treatment of skin TB.

**Microbiology**. Mycobacteria are aerobic, non-sporeforming, non-motile, facultative, intracellular, curved rods measuring 0.2-0.5 by 2.0-4.0 μm. Their cell walls contain mycolic acid-rich long-chain glycolipids and phospholipoglycans (mycocides) that protect mycobacteria from cell lysosomal attack and also retain red basic fuchsin dye after acid rinsing (acid-fast stain). The Ziehl-Neelson acid-fast stain, while highly specific for mycobacteria, is relatively insensitive, and detection requires at least 10,000 bacilli per mL; most clinical laboratories currently use a more sensitive auramine-rhodamine fluorescent stain (auramine O).

Routine culture uses a nonselective egg medium (Lowenstein-Jensen or Middlebrook 7H10) and often requires more than 3-4 weeks to grow because of the 22-hour doubling time of *M tuberculosis*. Radiometric broth culture (BACTEC radiometric system) of clinical specimens significantly reduces time (10-14 d) for mycobacterial recovery.

DNA probes specific for mycobacterial ribosomal RNA identify species of clinically significant isolates after recovery. In tissue, polymerase chain reaction (PCR) amplification techniques can be used to detect *M.tuberculosis*-specific DNA sequences and thus, small numbers of mycobacteria in clinical specimens.

**Pathophysiology. Disease transmission.**TB is an airborne communicable disease that occurs after inhalation of infectious droplets expelled from patients with laryngeal or pulmonary TB during coughing, sneezing, or speaking. Each cough can generate more than 3000 infectious droplets. Droplets are so small (1-5 μm) that they remain airborne for hours. The probability that disease transmission will occur depends upon the infectiousness of the tuberculous patient, the environment in which exposure takes place, and the duration of exposure. Approximately 20% of people in household contact develop infection (tuberculin skin test positive). Microepidemics have occurred in closed environments such as transcontinental flights and submarines. Tuberculin sensitivity develops 2-10 weeks after infection and usually is lifelong.

Without treatment, an approximate 10% lifetime chance exists of developing active disease after TB infection (5% within the first 2 years, 5% thereafter). Increased risk of acquiring active disease occurs with HIV infection (100-fold risk overall, 10% chance per year), IV drug abuse, diabetes mellitus (3-fold risk), silicosis, immunosuppressive therapy, cancer of the head and neck, hematologic malignancies, end-stage renal disease, intestinal bypass surgery or gastrectomy, chronic malabsorption syndromes, low body weight, and in infants younger than 2 years.

Because TB induces a strong immune response, individuals with positive tuberculin reactions are at a significantly lower risk of acquiring new TB infection. In HIV-infected individuals, active TB more likely occurs from reactivation of existing disease than from superinfection with a new mycobacterial strain.

**Pathogenesis.**The typical TB lesion is epithelioid granuloma with central caseation necrosis. The most common site of the primary lesion is within alveolar macrophages in subpleural regions of the lung. Bacilli proliferate locally and spread through the lymphatics to a hilar node, forming the Ghon complex. Early tubercles are spherical 0.5- to 3.0-mm nodules with 3 or 4 cellular zones demonstrating (1) a central caseation necrosis, (2) an inner cellular zone of epithelioid macrophages and Langhans giant cells admixed with lymphocytes, (3) an outer cellular zone of lymphocytes, plasma cells, and immature macrophages, and (4) a rim of fibrosis in healing lesions.

Initial lesions may heal and the infection becomes latent before symptomatic disease occurs. Smaller tubercles may resolve completely. Fibrosis occurs when hydrolytic enzymes dissolve tubercles, and larger lesions are surrounded by a fibrous capsule. Such fibrocaseous nodules usually contain viable mycobacteria and are potential lifelong foci for reactivation or cavitation. Some nodules calcify or ossify and are seen easily on chest x-ray. Tissues within areas of caseation necrosis have high levels of fatty acids, low pH, and low oxygen tension, all of which inhibit growth of the tubercle bacillus.

If the host is unable to arrest the initial infection, the patient develops progressive primary TB with tuberculous pneumonia in the lower and middle lobes of the lung. Purulent exudates with large numbers of acid-fast bacilli can be found in sputum and tissue. Subserosal granulomas may rupture into the pleural or pericardial spaces and create serous inflammation and effusions.

With the onset of host-immune response, lesions that develop around mycobacterial foci can be either proliferative or exudative. Both types of lesions develop in the same host, since infective dose and local immunity vary from site to site.

Proliferative lesions develop where the bacillary load is small and host cellular-immune responses dominate. These tubercles are compact with activated macrophages admixed and are surrounded by proliferating lymphocytes, plasma cells, and an outer rim of fibrosis. Intracellular killing of mycobacteria is effective, and the bacillary load remains low.

Exudative lesions predominate when large numbers of bacilli are present and host defenses are weak. These loose aggregates of immature macrophages, neutrophils, fibrin, and caseation necrosis are sites of mycobacterial growth. Without treatment, these lesions progress and infection spreads.

Although mycobacteria are spread by blood throughout the body during initial infection, primary extrapulmonary disease is rare except in severely immunocompromised hosts. Resistant hosts control mycobacterial growth at distant foci before development of active disease. Infants, older persons, or otherwise immunosuppressed hosts are unable to control mycobacterial growth and develop disseminated (primary miliary) TB. Patients who become immunocompromised months to years after primary infection also can develop late generalized disease.

The lungs are the most common site for TB disease: 85% of TB patients present with pulmonary complaints. Extrapulmonary TB can occur as part of a primary or late generalized infection or as a reactivation site that may coexist with pulmonary reactivation. The most common sites of extrapulmonary disease are mediastinal, retroperitoneal, and cervical (scrofula) lymph nodes, vertebral bodes, adrenals, meninges, and the GI tract. Pathology of these lesions is similar to those in the lung.

**Cutaneous tuberculosis.**Although 1 of 3 individuals on this planet is infected with tubercle bacillus, the incidence of cutaneous TB appears low. In areas such as India or China where TB prevalence is high, cutaneous manifestations of TB (overt infection or tuberculids) are found in fewer than 0.1% of individuals seen in dermatology clinics.

**Frequency.**The current global burden of TB boggles the mind. In 1997, the incidence of new TB patients approached 8,000,000 in addition to more than 16,000,000 existing patients. Approximately 2,000,000 people died of TB in 1997 with a global fatality rate of 23% (fatality rates exceed 50% in some African countries with high HIV incidence). The estimate of the proportion of TB patients with coincident HIV infection is approximately 8%. Among infectious diseases, TB is the leading cause of death. TB was responsible for 6% of deaths worldwide. Global prevalence of TB currently is greater than 32%. More than 50% of new patient occurrences were in 5 Asian countries, i.e. India (largest worldwide patient load), China, Indonesia, Bangladesh, and Pakistan.

**Age.**Although no age group is exempt, most patients show clinical infection within the first 3 decades of life.

**History.**The variants of cutaneous TB present as follows:

***Primary-inoculation TB (tuberculous chancre***). Primary-inoculation TB results from direct introduction of mycobacteria into the skin or mucosa of an individual who was not previously infected with TB or was immunized with the *M. bovis* strain bacille Calmette-Guérin (BCG). Since mycobacteria do not penetrate intact skin, initiation of infection almost always follows an injury, usually in children. Common sites include the face and other exposed skin. Tuberculous chancres are reported after ritual circumcision, tattooing, ear piercing, venipuncture, sexual

intercourse, tooth extraction, and after ingestion of milk contaminated with *M. bovis*. Primary-inoculation TB also is reported after *M.bovis* BCG immunotherapy for malignant melanoma. After mycobacteria gain entry into the skin, they multiply in tissue macrophages and spread to regional lymph nodes. An inflammatory papule develops in 2-4 weeks at the inoculation site that breaks down into a firm, non-healing, shallow, non-tender, undermined ulcer with a granulomatous base. Painless regional lymphadenopathy is evident at 3-8 weeks. Numerous bacilli are present at the inoculation site and regional node. This ulceroglandular complex is the skin analog to the Ghon complex.

As with all TB infections, the clinical course depends upon the host-immune response. Tuberculin sensitivity usually is coincident with the development of lymphadenopathy. Epithelioid granulomas are evident in the skin and lymph nodes. Numbers of tubercle bacilli progressively decrease. The primary lesion heals with scarring after 1-3 months. With a less effective host-immune response, bacterial load remains high and healing is delayed for up to 12 months. Regional nodes may suppurate, erode, and perforate the surface of overlying skin (scrofuloderma). Latent foci of infection can remain at the site and progress to lupus vulgaris or TB verrucosa cutis despite evident tuberculin sensitivity. Hematogenous dissemination of mycobacteria from skin can result in TB at other sites (particularly bones and joints) or progress catastrophically to acute miliary disease with a fatal outcome.

***TB verrucosa cutis.*** TB verrucosa cutis is an indolent warty plaque that occurs after direct inoculation of TB into the skin of individuals previously infected with *M. tuberculosis* or *M. bovis*. Reinfection TB can result from accidental exposure to tuberculous tissue in high-risk groups, such as physicians, pathologists, and laboratory workers (anatomists' wart, prosectors' wart, verruca necrogenica). Farmers, butchers, and veterinarians contract this form of reinfection TB from tuberculous cattle. Individuals, especially children from lower socioeconomic groups, also can contract this lesion after contact with tuberculous sputum. In countries such as India, walking barefoot and the habit of spitting associated with betel leaf (paan) chewing are worth noting.

Lesions most commonly occur on the hands and, in children, the lower extremities. Infection starts as an asymptomatic warty papule often mistaken for verruca vulgaris. Slow growth and irregular peripheral extension occur. The lesion may show central involution with an atrophic scar or form massive papillary excrescence with fissures. Pus and keratinous material may extrude from these fissures. Lesions usually are solitary, and regional nodes are not affected unless secondary bacterial infection occurs. Lesions may evolve and persist for years. Spontaneous resolution with scarring can occur.

Histology shows pseudoepitheliomatous hyperplasia with marked hyperkeratosis and a dense inflammatory infiltrate of neutrophils and lymphocytes. Abscesses form in the superficial dermis and epidermis. Epithelioid giant cells occur, but typical tubercles and acid-fast bacilli are rare.

***Miliary TB of the skin.*** Miliary TB of the skin is a rare manifestation of fulminant miliary TB resulting from hematogenous spread of mycobacteria to multiple organs, including skin. The initial site of infection usually is pulmonary or meningeal. This disease occurs predominantly in children and may be coincident with other infections such as measles. Tuberculin sensitivity is absent and bacillary load is high, which is consistent with an overwhelming infection. Currently, numerous instances of miliary TB of the skin are reported in immunosuppressed individuals infected with HIV. Disseminated lesions occur on all parts of the body, especially the trunk. Lesions erupt as small (millet-sized) red macules or papules. Purpura, vesicles, and central necrosis are common. Histologically, lesions show microabscesses with tissue necrosis and nonspecific inflammatory infiltrates. Tubercle bacilli are numerous and are demonstrated in tissue and intravascular spaces. Affected patients are gravely ill, and the prognosis is poor.

***Scrofuloderma.*** Scrofuloderma results from breakdown of skin overlying a tuberculous focus, usually at a lymph node but also at the skin over infected bones or joints. Historically, a high prevalence of scrofuloderma was seen in children infected with *M. bovis* from contaminated milk. The oral or tonsillar primary lesion progresses to cervical adenitis, formation of cold abscesses, and secondary breakdown of overlying skin. Lesions present as firm, painless, subcutaneous nodules that gradually enlarge and suppurate, then form ulcers and sinus tracts in overlying skin. Typical ulcers have undermined edges and a floor of granulation tissue. Typical tubercles with acid-fast bacilli are found in the lower dermis and walls of the ulcer or abscess. Tubercle bacilli usually can be isolated from the purulent discharge. Tuberculin sensitivity usually is marked. Spontaneous healing can occur but often takes years and is accompanied by the formation of hypertrophic scars. Lupus vulgaris may develop in the vicinity of healing scrofuloderma.

Metastatic tuberculous abscess (tuberculous gumma) is a variant of scrofuloderma that occurs following hematogenous spread of mycobacteria to skin in tuberculin-sensitive individuals. Painless, fluctuant, subcutaneous abscesses form singly or at multiple sites, then break down into fistulas and ulcers resembling scrofuloderma. Typically, these lesions occur in malnourished children or in severely immunosuppressed patients.

***TB cutis orificialis.*** Orificial TB results from autoinoculation of mycobacteria into the periorificial skin and mucous membranes in patients with advanced TB. Underlying disease can be pulmonary, intestinal, or genitourinary TB. Infectious mycobacteria shed from these foci are inoculated into surrounding mucous membranes and skin. Patients typically are older men. Tuberculin sensitivity is strong. The site of the periorificial lesion often is determined by trauma.

In orificial TB, the tip and lateral margins of the tongue are affected most frequently; however, hard and soft palate lesions also are common. Autoinoculation of tooth sockets can occur after extraction. Perianal skin, the vulva, the urinary meatus, and the glans penis also are described sites. Lesions start as red papules that evolve into painful, soft, punched-out, shallow ulcers.

Tubercles with acid-fast bacilli can be found in the deep dermis and ulcer walls. Usually, patients that develop orificial TB have severe internal organ disease and the appearance of these lesions portends a poor prognosis.

***Lupus vulgaris.*** Lupus vulgaris is a chronic and progressive form of cutaneous TB that occurs in tuberculin-sensitive patients. In most series, it is the most common form of cutaneous TB and has the most variable presentation. Lesions appear in normal skin as a result of direct extension of underlying tuberculous foci, of lymphatic or hematogenous spread, after primary inoculation, BCG vaccination, or in scars of old scrofuloderma. Historically, lupus vulgaris was most prevalent in northern Europe (cause of lower prevalence in Asian countries is not known), with affected females outnumbering males by 2-3:1.Lesions usually are solitary, and more than 90% involve the head and neck. Small, sharply marginated, red-brown papules of gelatinous consistency (apple-jelly nodules) slowly evolve by peripheral extension and central atrophy into large plaques. However, many clinicians in Asian countries who see large numbers of this entity have questioned the descriptive term "apple jelly nodules," since this is not seen in many pigmented patients. Reappearance of new nodules within previously atrophic or scarred lesions is characteristic. Cartilage (nose, ears) within the affected area is progressively destroyed (lupus vorax); bone usually is spared. Buccal, nasal, and conjunctival mucosas may be involved primarily or by extension.

Clinical variants are numerous and are seen in the following forms:

*Plaque forms*: disease extension occurs with little central atrophy. Scaling can occur, especially on the lower legs where it may resemble psoriasis. Irregular scarring is common and the active edge may be thickened and hyperkeratotic.

*Ulcerating form*: scarring and ulceration predominate. Crusts form over areas of necrosis. Deep tissues and cartilage are invaded by eventual scarring that produces contractures and deformity.

*Vegetative form*: this form is characterized by necrosis, ulceration, and proliferative and papillomatous granulation tissue.

*Nodular form*: this form is characterized by a relative absence of ulceration and scarring. Large soft tumors occur, especially on ear lobes.

Histologically, the most prominent feature is a typical granulomatous tubercle with epithelioid cells, Langhans giant cells, and a mononuclear infiltrate. Caseation necrosis is minimal, and acid-fast bacilli are rare. Tissue histology varies with secondary changes of abscess formation, ulceration, atrophy, and scarring.

Lesions often persist for years before diagnosis and can be disfiguring. Patients with lupus vulgaris and pulmonary TB have a 4- to 10-fold higher mortality than with pulmonary TB alone. In long-standing lupus vulgaris, squamous cell carcinoma can occur and be confused with the disease itself.

***Tuberculids***: tuberculids are symmetric generalized exanthemas in the skin of tuberculous patients, possibly resulting from hypersensitivity reactions to tubercle bacillus. Typically, patients with tuberculids are in relatively good health and show (1) positive tuberculin sensitivity, (2) tuberculous involvement (usually inactive) of viscera or lymph nodes, (3) negative staining and culture for pathogenic

mycobacteria in affected tissue, and (4) skin lesions that heal with remission or treatment of TB. Originally, these exanthemas were believed secondary to mycobacterial "toxins"; however, recent opinion and identification of mycobacterial DNA by PCR amplification reactions in affected tissue suggest that they are manifestations of hematogenous spread of bacilli in patients with tuberculin immunity.

***Erythema induratum (Bazin disease).*** Erythema induratum is a persistent or recurring condition associated with past or active TB. Inflammatory cutaneous and subcutaneous nodules that may ulcerate and scar occur in the posterior calves of women's legs (<10% of affected patients are men). Preexisting erythrocyanotic circulatory disease may predispose patients to lesions. Cutis marmorata is common, and an increased prevalence is seen during cold weather.

Lesions arise in small numbers as tender indurated plaques and nodules that may progress to ulceration and scarring. In early stages, inflammation occurs in venous walls with adventitial thickening and endothelial proliferation. A perivascular inflammatory infiltrate also may be present. Septal panniculitis is present, which may extend into fat lobules. Fat necrosis and foreign-body giant cells occur, and fibrosis and atrophy (wucher atrophy) replace subcutaneous fat. Tubercle bacilli are not seen, and mycobacterial cultures usually are negative. Erythema induratum often recurs for years.

***Papulonecrotic tuberculid*** occurs as a chronic and recurrent symmetric eruption of necrotizing skin papules appearing in clusters and healing with varioliform scars. Tubercle bacilli are difficult to demonstrate, but patients usually have an internal focus of TB and are tuberculin sensitive, and skin lesions resolve after anti-TB therapy. Recent studies detected TB DNA in these lesions using PCR amplification reactions. Lesions appear on the exterior aspects of extremities (knees, elbows, buttocks, lower trunk) in a symmetric distribution, often in clusters. Individual lesions are asymptomatic, small, dusky red papules with a central punctum or crust. Involution is common after 6-8 weeks and leaves pitted scars.

Histologically, these lesions show a wedge-shaped necrosis of the upper dermis extending to and involving the epidermis. Epithelioid cells and, infrequently, Langhans giant cells are seen. An obliterative granulomatous vasculitis with fibrin present in vessel walls and lumen is typical.

***Lichen scrofulosorum*** is an eruption of asymptomatic, grouped, closely set, 1-2 mm, perifollicular, lichenoid papules affecting children and young adults with underlying TB. The eruption becomes more extensive for weeks, then slowly regresses for months without scarring. Recurrences are possible. The response to anti-TB drugs is not as remarkable as that seen in other tuberculids.

Histologically, tuberculoid granulomas can be seen surrounding hair follicles and sweat ducts. Caseation necrosis usually is absent. No acid-fast bacilli are seen.

**Lab Studies.** Workup for cutaneous TB forms is directed against the underlying systemic disease.Obtain a medical history for symptoms of the disease, TB exposure or infection, past TB treatment, demographic risk factors for TB, and

medical conditions that increase risk for TB. Perform a physical examination. Perform a tuberculin skin test.

**Imaging Studies.** Obtain a posteroanterior chest radiograph.

**Other Tests.**Obtain specimens for bacteriologic examination: 3 sputum specimens on each of 3 consecutive days.Alternatively, obtain specimens for histologic examination: acid-fast bacilli in stained tissue or nucleic acid amplification of bacterial DNA and RNA.Perform a deep biopsy for suspected lupus vulgaris.

**Medical Care.**Isolate patients with possible TB infection in a private room with negative pressure (air exhausted to outside or through a high-efficiency particulate air filter). Medical staff must wear high-efficiency disposable masks sufficient to filter the tubercle bacillus. Continue isolation until sputum smears are negative for 3 consecutive determinations (usually after approximately 2-4 weeks of treatment). Unfortunately, these measures are neither possible nor practical in countries where TB is a public health problem.

Treatment regimens adequate for pulmonary TB also are effective for extrapulmonary disease. Treat infants and children with miliary TB, bone or joint TB, or TB meningitis for a minimum of 12 weeks.

Because of increased drug resistance among TB isolates, TB treatment regimens must contain multiple drugs to which the isolated bacillus is susceptible. These regimens must be taken regularly and for a sufficient period.

In most patients, initiate anti-TB treatment with a 4-drug regimen and include ethambutol or streptomycin in the initial regimen until results of drug susceptibility are known or the chance of drug resistance is minimized. Low risk of drug resistance may be indicated as (1) less than 4% primary drug resistance to isoniazid in the local community, (2) the patient has had no previous treatment with TB drugs, (3) the patient is not from a country with high prevalence of drug-resistant TB, and (4) the patient has no known exposure to a person with drug-resistant TB.

Short-course therapy (for drug-susceptible strains in HIV-seronegative patients) lasts for 6 months.

The initial phase of 4-drug treatment is for 2 months. The drugs are used as follows:

☐ Isoniazid: 5 mg/kg/d in adults; 10-20 mg/kg/d in children, not to exceed 300 mg qd

☐ Rifampin: 10 mg/kg/d in adults; 10-20 mg/kg/d in children, not to exceed 600 mg qd

☐ Pyrazinamide: 15-30 mg/kg/d in adults and children, not to exceed 2000 mg qd

☐ Ethambutol: 15-25 mg/kg/d in adults and children or streptomycin: 15 mg/kg/d in adults; 20-40 mg/kg/d in children, not to exceed 1000 mg qd

If TB isolates are susceptible to isoniazid and rifampin, the second phase of treatment consists of isoniazid and rifampin for 4 months.

Consider directly observed therapy (DOT) for patients with active disease. This intermittent treatment under direct observation significantly increases cure rate, decreases transmission of disease, and prevents emergence of multidrug resistant TB. DOT has been designed to prevent irregularity in drug intake in TB patients.

The 4-drug DOT administered daily for 2 months can be followed by treatment with isoniazid and rifampin administered 2 or 3 times per week.
Four-drug DOT can be administered daily for 2 weeks, then 2 times per week for 6 weeks, followed by isoniazid and rifampin alone 2 times per week for 16 weeks.
Four-drug DOT can be administered 3 times per week throughout the 6-month treatment period.
Treat drug-resistant strains of tubercle bacilli in consultation with experienced physicians. Additional anti-TB drugs and longer treatment intervals often are needed. Daily DOT is recommended.
Drugs used for this variant include kanamycin, amikacin, capreomycin, ciprofloxacin, ofloxacin, sparfloxacin, ethionamide, and prothionamide.
**Surgical Care.**The role of surgery in cutaneous TB is limited. However, hypertrophic and verrucous lesions of lupus vulgaris and TB verrucosa cutis have been treated with electrosurgery, cryosurgery, and curettage with electrodesiccation as an adjunct measure, with pharmacologic therapy as the primary method of treatment.

# XII. PARASITIC INFECTIONS

## 12.1. Scabies

**Background.**Scabies is an intensely pruritic, highly contagious infestation of the skin by the arachnid mite *Sarcoptes scabiei,* variety *hominis*. Originally, scabies was a term used by the Romans to denote any pruritic skin disease. In the 17th century, Giovanni Cosimo Bonomo identified the mite as one cause of scabies. The name *S. scabiei* is derived from the Greek words *sarx* (the flesh) and *koptein* (to smite or cut) and the Latin word *scabere* (to scratch). Today, the term scabies refers to the skin lesions produced by this mite.

Scabies has played an important role in world history, with epidemics partially coinciding with military activities and major social upheavals. Scabies has been recognized as a disease for approximately 2500 years. Historically, it was treated with topical sulfur, a treatment still in use today.

Like syphilis, scabies has come to be known as the great imitator. Its spectrum of clinical manifestations may lead the practitioner to the wrong diagnosis. The phrase "7-year itch" was first used with reference to persistent, undiagnosed infestations with scabies, not as a movie title.

**Pathophysiology.**The mite, *S. scabiei,* spreads disease through direct and prolonged contact with the host. The mite remains viable for 2-5 days on inanimate objects; therefore, transmission through fomites, such as infected bedding or clothing, is possible, but less likely. Once bound to their host, 10-15 mites mate on the surface of the skin.

After mating, the male mite dies. The female mite burrows into the epidermis of the host using her jaws and front legs, where she lays up to 3 eggs per day for the duration of her 30- to 60-day lifetime. An affected host harbors approximately 11 adult female mites during a typical infestation. The eggs hatch in 3-4 days. The larvae leave the burrow to mature on the skin. Fewer than 10% of the eggs laid result in mature mites.

A delayed type IV hypersensitivity reaction to the mites, their eggs, or scybala (packets of feces) occurs approximately 30 days after infestation. This reaction is responsible for the intense pruritus, which is the hallmark of the disease. Individuals who are already sensitized from a prior infestation can develop symptoms within hours.

Scabies is usually transmitted by direct contact with an affected individual. Although disputed, some believe one can become infested by indirect contact with the personal items or clothing of an affected person because the mite can survive away from the skin for 2-5 days. This is much more likely to occur in the environment of someone with crusted or hyperkeratotic scabies.

In 1848, Norwegians Danielssen and Boeck described a highly contagious variant of scabies that occurs in immunocompromised patients. Crusted or hyperkeratotic scabies, as it has come to be known, is an overwhelming scabies infestation. This

rare form of scabies occurs in elderly or mentally incompetent patients. Because of an impaired antibody response, these individuals can be infested with thousands to a couple million mites.

**Causes.**Human scabies is caused by the arachnid itch mite, *S. scabiei* (var *hominis*). Animals can transmit nonhuman scabies to people. Human infestation with animal scabies is known to be self-limiting, and, clinically, burrows are often absent. Cases have been documented of transmission from horses, cattle, goats, camels, llamas, sheep, foxes, and, most commonly, dogs. In fact, canine scabies is known as mange. One of the causative agents of animal scabies is *Cheyletiella yasguri*.

**Frequency.** In undeveloped countries, scabies infestation is pandemic, with millions affected worldwide.

**Mortality/Morbidity.**Scabies is unlikely to cause a long-term disease state in healthy individuals. However, without adequate treatment, the lesions and associated pruritus may last for weeks to months. Immunocompromised individuals are likely to develop crusted scabies, which may be impossible to fully eradicate. Those infested may contract secondary bacterial infections via skin abrasion due to excessive scratching. These secondary infections may result in cellulitis, lymphangitis, and acute glomerulonephritis. Other than deaths related to secondary infection, scabies causes no appreciable mortality.

**Age.**Disease is more common in children (<15 y), young adults (associated with sexual contact), immunocompromised persons, and elderly patients (especially those who are institutionalized or bedridden).

**History.**Consider the diagnosis of scabies in any patient presenting with a recent onset of intense itching, especially at night.An increase in the intensity of the pruritus often forces the patient to seek medical attention.Importantly, attempt to elicit a history of pruritus in family members, sexual partners, close contacts, and pets.Itching usually spares the head and neck but can be localized anywhere else on the body. However, in infants and young children, the lesions are localized to the face, neck, trunk, palms, and soles. Patients with crusted scabies may itch only 50% of the time.Tenderness of the lesions suggests secondary bacterial infection.

**Physical.**Findings include both primary lesions and secondary lesions. Each category has its own distinguishing characteristics.

***Primary lesions.*** The distribution of lesions is highly characteristic in typical scabies in adults.The burrow appears as a straight, curved, or S-shaped line. It is usually 2-5 millimeters long, slightly elevated, and pinkish-white. A black dot may be seen at one end of the burrow, indicating the presence of a mite. Common locations include the webbed spaces of the fingers, flexor surfaces of the wrists, elbows, axillae, belt line, feet, and scrotum in men and areolae in women. In infants, burrows are commonly located on the palms and soles.

Vesicles and papules can be seen near burrows or alone. Vesicles appear as discrete lesions filled with serous rather than purulent fluid. The individual character of the lesion is indicative of scabies rather than other skin disorders, which have grouped vesicular manifestations (e.g. poison ivy). Papules rarely

contain mites and most likely are due to a hypersensitivity reaction. Papules are common on the shaft of the penis in men. (Note: Canine scabies, scabies in humans due to the canine mite, usually manifests with vesicles and papules, not the classic burrow). Crusted scabies is an atypical form of scabies occurring in immunocompromised and institutionalized populations. Lesions are often hyperkeratotic, crusted, and cover large areas. Marked scaling is common, and pruritus can be minimal. Nail dystrophy and scalp lesions may be prominent. Nodular scabies occurs in 7-10% of patients with scabies. Pink, tan, brown, or red nodules can be seen. They range from 2-20 millimeters in diameter. The mite is not usually present within the nodular lesion.

***Secondary lesions.*** These are usually the result of excessive scratching. Characteristic findings include excoriations, postinflammatory hyperpigmentation, generalized eczematous dermatitis, erythroderma, prurigo-like lesions, and pyoderma.

**Complications.**Treatment failures are uncommon if guidelines are followed.Residual pruritus may require antihistamines or a short course of topical or oral corticosteroids.Secondary infection may require antibiotics.Scabetic nodules may require intranodular corticosteroid injection.

**Lab Studies.**The most common and useful technique used to diagnose scabies is examination of skin scrapings under light microscopy. A definitive diagnosis is made if the scraping contains a mite, larvae, eggs, or fecal pellets.

**Other Tests.** Elevated immunoglobulin E titers and eosinophilia may be demonstrated in some patients with scabies.Defective immune function, especially in individuals with HIV disease, may be associated with hyperkeratotic scabies.

**Procedures.** The best sample can be obtained by scraping a burrow or unexcoriated papule. Asking the patient to identify an actively pruritic lesion may be helpful.A drop of mineral oil is placed on the lesion. Then, a sterile blade is used to gently scrape the burrow or papule. The lesion should be scraped 6-7 times, and bleeding should be avoided.The skin scrapings are placed on a glass slide and examined under a light microscope at 40X magnification.The burrow ink test can also be used to make the diagnosis of scabies. The tip of a fountain pen is rubbed along the site of a possible burrow. The ink penetrates the burrow, distinguishing it from the surrounding tissue. The excess ink is wiped off with an alcohol pad. This technique is particularly useful in children and individuals with very few burrows.Use of topical tetracycline solution is an alternative to the burrow ink test. After application and removal of the excess tetracycline solution with alcohol, the burrow is examined under a Wood light. The remaining tetracycline fluoresces a greenish color. This method is preferred because tetracycline is a colorless solution and large areas of skin can be covered.When diagnosing crusted scabies, 10% potassium hydroxide is added to the skin scraping, which permits adequate microscopic viewing by decreasing the amount of keratitic debris.A past history of scabies is important when diagnosing nodular scabies.

**Histologic Findings.**A burrow containing the female mite and ova within stratum corneum may or may not be present. An inflammatory infiltrate in the deep and

superficial dermis is composed of lymphocytes, histiocytes, eosinophils, and occasional neutrophils. Spongiosis and vesicle formation is present near the mite.
Crusted scabies also demonstrates an inflammatory infiltrate. However, it is coupled with prominent hyperkeratosis and innumerable mites.
Nodular scabies reveals a dense, mixed, inflammatory cell infiltrate. The infiltrate is noted around blood vessels of the dermis and subcutaneous fat. Atypical mononuclear cells may be present. Mites are not a common finding.
**Medical Care.**Treat with a scabicide. Provide antihistamines to help alleviate pruritus. Use appropriate antibiotics for the treatment of secondary infections. For crusted scabies, crust and scale removal is necessary for scabicide penetration. All family members and close contacts of those diagnosed with scabies must receive treatment. Instruct patients to wash bed linens, clothing, and towels in warm water.
Symptomatic treatment may require oral antihistamines and topical antipruritics/anesthetics such as menthol (Sarna lotion) and pramoxine (Prax). More severe symptoms may require a short course of topical or oral steroids. Secondary infections may require antibiotics. Oral ivermectin can be used in cases for which topical therapy is difficult or impractical (e.g. widespread infestations in nursing homes).
Permethrin (Elimite) - 5% cream. DOC, especially for infants >2 months and small children. More effective than crotamiton for treating symptoms and reducing chances of secondary bacterial infection. Even after successful treatment, postscabietic nodules and pruritus may persist for months. Sulfur in petrolatum - 10% concentration. One of few effective scabicidal treatments that may be used safely without fear of toxicity in very small children and pregnant women. Crotamiton (Eurax) - 10% lotion or cream. Mechanism of action is unknown. Ivermectin (Mectizan, Stromectol) - binds selectively with glutamate-gated chloride ion channels in invertebrate nerve and muscle cells, causing cell death.
**Activity.**Infected individuals should avoid skin-to-skin contact with uninfected individuals. Decontamination of clothing, bed linens, and other personal items must coincide with medical treatment.
**Prevention.**All household members and close personal contacts older than 2 months and not pregnant should be treated, regardless of whether they are symptomatic.Patients should be reexamined 2-4 weeks after treatment to evaluate effectiveness.If itching persists 1 week after the initial treatment, a second treatment may be indicated. Rarely, individuals with a history of atopy may require a tapered dose of prednisone for the treatment of severe pruritus. Intranodular injection of dilute corticosteroids may be indicated with nodular scabies. Because of the presence of innumerable mites, crusted scabies may require repeated applications of scabicide or oral ivermectin. Importantly, inform patients that the resolution of symptoms may require weeks.
**Prognosis.**Prognosis is excellent with proper diagnosis and treatment unless the patient is immunocompromised or institutionalized. These individuals are at an increased risk for crusted scabies, which is associated with a less favorable outcome.

## 12.2. Leishmaniasis

**Background:** Leishmaniasis is a disease caused by protozoa, and it affects as many as 12 million people worldwide, with 1.5-2 million new cases each year. The global incidence of this infectious disease has increased in recent years because of increased international leisure and military related travel, human alteration of vector habitats, and concomitant factors that increase susceptibility, such as HIV infection and malnutrition. The recent conflicts in Iraq, Kuwait, and Afghanistan have led to >600 cases of cutaneous leishmaniasis and 4 cases of visceral leishmaniasis (VL) in American soldiers in 2004 alone.

Transmitted by the bite of a sandfly, the clinical spectrum of leishmaniasis ranges from a self-resolving cutaneous ulcer to a mutilating mucocutaneous disease to a lethal systemic illness.

Many *Leishmania* species transmit the disease, and the clinical spectrum, although once believed to be predictable, continues to evolve. Diagnosis may be difficult because of the small size of the protozoa sequestered within macrophages of the skin, bone marrow, and reticuloendothelial system. Therapy has long been a challenge in the more severe forms of the disease and is made more difficult by the emergence of drug resistance. No effective vaccine for leishmaniasis is available.

**Pathophysiology.**Mammalian reservoirs for leishmanial parasites include rodents, canines, equines, monkeys, sloths, and humans. In mammalian hosts, the organism exists as a nonflagellated amastigote composed of a large nucleus and a smaller kinetoplast that resides in the phagolysosome of the macrophage. The vector sandfly, of the genus *Phlebotomus* in the Old World and of the genus *Lutzomyia* in the New World, ingests the amastigotes when drawing a blood meal from an infected host. In the gut of the sandfly, the protozoa multiply and transform into flagellated promastigotes.

The promastigotes migrate to the proboscis of the sandfly and are inoculated into the naive host during the insect's next blood meal. The promastigotes enter the new host's macrophages, where they transform back into amastigotes, multiply, and spread throughout the reticuloendothelial system. Clinical disease is apparent within weeks to months after infection.

Similar to Hansen disease, leishmaniasis is a disease in which the clinical diversity reflects a complex interplay between the virulence of the infecting species and the host's immune response. At one extreme, localized cutaneous disease demonstrates a vigorous immune response, with most cases resolving without intervention. This form of disease exhibits a helper T-cell subtype 1 (TH1) immune response, with interleukin-2, interferon-gamma, and interleukin-12 as the prominent cytokines that induce disease resolution. At the other extreme, with visceral or diffuse cutaneous disease, patients exhibit relative anergy to the *Leishmania* organism and have a prominent helper T-cell subtype 2 (TH2) cytokine profile. The immunomodulation of leishmaniasis has become an area of intense study in the search for new treatments for this disease.

**Frequency.**Leishmaniasis occurs in temperate and tropical climates in all parts of the world except Australia and Oceania (Pacific islands of Melanesia, Micronesia, and Polynesia). The vast majority of cutaneous cases occur in Afghanistan, Algeria, Brazil, Peru, Iran, Iraq, Syria, and Saudi Arabia, whereas most visceral cases occur in India, Bangladesh, Nepal, Brazil, and the Sudan. The sandfly vector is adept at adjusting to climatic changes and to pressures of human habitation; therefore, vigilant epidemiologic tracking is required to monitor new patterns of disease prevalence. Most cases of leishmaniasis in the United States are imported from elsewhere. Sporadic endemic transmission of cutaneous disease has been reported in rural southern Texas.

**Mortality/Morbidity.**As many as 90% of localized cutaneous forms of leishmaniasis heal spontaneously with scarring. Disseminated, recidivans, and post–kala azar forms of cutaneous leishmaniasis can be disfiguring cosmetically because of the degree of persistent involvement; however, these forms are not life threatening. Mucocutaneous leishmaniasis (MCL) can result in extensive midfacial mutilation and, occasionally, death resulting from airway or nutritional compromise. VL (kala azar) is a serious potentially lethal systemic illness. Epidemics of kala azar in impoverished communities can result in death in the majority of untreated patients.

**Age.**No specific age susceptibility is known; however, individuals at the extremes of age may be less able to mount effective immune response to infection. *Leishmania infantum* produces an infantile form of VL. An apparent predilection for the young appears to occur in highly endemic areas because of what may be protective immunity protecting adults from reinfection.

**History.**The discovery of parasites in lesions of cutaneous or VL was reported in the late 1800s and early 1900s. By the mid 1900s, the transmission and life cycle of the *Leishmania* organism had been confirmed scientifically. Since that time, many clinical syndromes and numerous (at least 20) morphologically similar species and subspecies of the protozoan have been, and continue to be, discovered. The taxonomy of *Leishmania* organisms is complex, and no single categorization is generally accepted.

The 2 simplest and most widely used disease categorization systems are based on clinical disease and geographic occurrence.

Clinical disease. The 3 primary clinical forms of leishmaniasis are cutaneous, mucocutaneous, and visceral disease. Cutaneous leishmaniasis can be further divided into localized, diffuse cutaneous, recidivans, and post–kala azar dermal leishmaniasis (PKADL).

Geographic occurrence. Old World leishmaniasis is caused by *Leishmania* species found in Africa, Asia, the Middle East, the Mediterranean, and India, and it produces cutaneous or visceral disease. New World leishmaniasis is caused by *Leishmania* species found in Central America and South America, and it produces cutaneous, mucocutaneous, and visceral disease.

The following forms of leishmaniasis have been identified:

***Localized cutaneous leishmaniasis*** (LCL): crusted papules or ulcers occur several weeks to months (and in rare cases) after sandfly bite inoculation on exposed skin. Lesions may be associated with sporotrichotic spread and usually heal spontaneously.

***Diffuse cutaneous leishmaniasis*** (DCL): analogous to lepromatous leprosy, individuals with DCL cannot mount a cell-mediated immune response to the *Leishmania* parasite. Consequently, patients develop multiple, widespread cutaneous papules and nodules, and they are anergic to leishmanin skin testing (LST).

***Recidivans cutaneous leishmaniasis*** (RCL): a relatively uncommon clinical variant of leishmaniasis, RCL appears as a recurrence of lesions at the site of apparently healed disease years after the original infection. RCL lesions typically occur on the face, and RCL presents as an enlarging papule, plaque, or coalescence of papules that heals with central scarring. Relentless expansion at the periphery may cause significant facial destruction similar to the lupus vulgaris variant of cutaneous tuberculosis.

***Post–kala azar dermal leishmaniasis*** (PKADL): endemic to India and the Sudan, this form of leishmaniasis develops months to years after the patient's recovery from VL. Cutaneous lesions demonstrate great variability, ranging from hypopigmented macules to erythematous papules and from nodules to plaques. As in leprosy, the wide clinical spectrum of PKADL reflects the immune response of the individual to the *Leishmania* organism. Lesions may be numerous and persist for decades. Isolated parasites from the lesions are identical to those causing the original visceral disease.

***Mucocutaneous leishmaniasis (MCL)***: predominantly a New World disease, this form of leishmaniasis may not manifest clinically until years after localized cutaneous disease apparently has healed. In a poorly understood manner, certain species of *Leishmania* migrate to the upper respiratory tract where relentless destruction of the oropharynx and nose ensues. Gradually, the migration results in extensive mid facial destruction and, occasionally, in death.

***Visceral leishmaniasis***(VL,kala azar): *Leishmania* parasites localize to the reticuloendothelial system, rather than to the skin, and produce a potentially lethal widespread systemic disease.

**Physical:** localized cutaneous leishmaniasis usually presents as a nonspecific ulcer that can mimic many those of other infectious and noninfectious skin conditions. The vast majority of cases heal spontaneously with scarring and never come to the attention of clinicians. In both the localized cutaneous and mucocutaneous forms of leishmaniasis, cell-mediated immunity to the parasite is vigorous and organism density in the skin and/or mucosa is low, especially in long-standing disease. Therefore, growing organisms in culture can be difficult, as can finding them in pathological specimens. Malnourished individuals are at greater risk of acquiring leishmaniasis and respond less well to treatment than those with adequate nutrition. Approximately 1-3% of individuals infected by *L. brasiliensis,* and a smaller percentage of individuals infected by *L. panamensis* and *L. guyanensis,* develop

mucosal metastases several months to years after the apparent resolution of cutaneous disease. Without treatment, destruction of the oral and nasopharyngeal mucosae is relentless. Symptoms of visceral leishmaniasis can be confused with many other infectious diseases; however, in endemic areas, the typical patient has wasting and presents with massive splenomegaly, pancytopenia, hypergammaglobulinemia, and intermittent fevers (though they are less acutely ill than patients with malaria).

***LCL***: a typical lesion begins as an inflammatory papule that later progresses to an ulcer. This may be associated with sporotrichotic lymphatic spread. In the vast majority of cases, the ulcers heal spontaneously with scarring.

***DCL***: patients develop hundreds of papules, nodules, and plaques throughout the skin in a clinical picture that can be reminiscent of lepromatous leprosy. This form of leishmaniasis often is resistant to therapy and may assume a chronic course.

***RCL***: typically, psoriasiform plaques occur on the face and progress centrifugally, bearing a striking resemblance to lupus vulgaris. Similar to disseminated disease, RCL may be resistant to therapy and result in a disfiguring clinical picture.

***PKADL***: cutaneous lesions are polymorphous, ranging from hypopigmented or erythematous macules to papules and nodules that may coalesce. Similar to DCL, PKADL closely resembles lepromatous leprosy. Prolonged intensive treatment is required to treat this disfiguring, but usually not lethal, form of leishmaniasis.

***MCL***: when left untreated, this form of leishmaniasis gradually spreads and results in extensive mid facial mutilation or, in some cases, in death.

***VL***: the hallmarks of this form are fever, malaise, hepatosplenomegaly, anorexia, wasting, pancytopenia, and hypergammaglobulinemia. Occasionally, the skin becomes severely xerotic and hyperpigmented because of melanocyte stimulation. This form of leishmaniasis frequently is lethal if not treated.

**Complications.**Secondary bacterial infection may occur.Leishmaniasis may be disfiguring.

**Causes.**In the vast majority of cases, sandfly bites transmit leishmaniasis; however, infection may be transmitted via a congenital route or through blood transfusions and contaminated needle sticks.

***Cutaneous leishmaniasis***

Localized cutaneous leishmaniasis. Old World: *Leishmania major, Leishmania tropica, Leishmania aethiopica,* and *L. infantum*. New World: *Leishmania mexicana, Leishmania venezuelensis, Leishmania amazonensis, Leishmania braziliensis, Leishmania panamensis, Leishmania guyanensis, Leishmania peruviana,* and *Leishmania chagasi.*

Diffuse cutaneous leishmaniasis. Old World: *L. aethiopica.*New World: *L. mexicana, L. amazonensis,* and *L. venezuelensis.*

Recidivans cutaneous leishmaniasis. Old World: *L. tropica*. New World: *L. braziliensis.*

Post–kala azar dermal leishmaniasis. Old World: *Leishmania donovani* and *L. infantum.*New World: *L. chagasi*

***Mucocutaneous leishmaniasis***

Old World: *L. aethiopica* (rare) and *L. major*. New World: *L. mexicana, L. amazonensis, L. braziliensis, L. guyanensis,* and *L. panamensis.*

***Visceral leishmaniasis***

Old World: *L. infantum, L. donovani,* and *L. tropica* (rare; also may produce the atypical viscerotropic disease). New World: *L. chagasi.*

***Other diagnostic considerations***

Differential diagnosis of LCL is extensive and includes impetigo, pyoderma gangrenosum, deep fungal infection, mycobacterial infection, sarcoidosis, and squamous cell carcinoma.

DCL and PKADL closely resemble lepromatous leprosy.RCL may mimic cutaneous tuberculosis (lupus vulgaris, tuberculosis verrucosa cutis), psoriasis, deep fungal infection, or nummular dermatitis.MCL may simulate paracoccidioidomycosis, histoplasmosis, syphilis, yaws, rhinoscleroma, squamous cell carcinoma, and midline granuloma of the face.VL may be confused with a variety of other infectious diseases or febrile systemic illnesses, including schistosomiasis, malaria, tropical splenomegaly syndrome, histoplasmosis, malnutrition, typhoid fever, brucellosis, miliary tuberculosis, lymphoma, leukemia, African trypanosomiasis, and bacterial endocarditis.Coexisting infectious diseases and/or nutritional deficiencies may impact the severity and outcome of leishmanial infection significantly. In southern Europe, VL is emerging most notably as a serious opportunistic infection in individuals with HIV infection. Co-infection by HIV and leishmanial organisms is particularly common in southern Europe along the Mediterranean where most adult patients (<70%) with visceral leishmaniasis are associated with late-stage AIDS. Individuals with HIV infection and leishmaniasis have higher parasite loads, poorer responses to skin testing, lower responses to pentavalent antimony, and higher posttreatment relapse rates than those of their immunocompetent counterparts.

**Lab Studies.*Cutaneous lesions***. Skin scrapings are obtained from the base of an active ulcer or biopsy of the edge of a suspicious lesion or ulcer. Leishmanial amastigotes may be identified from cutaneous lesions or in biopsy specimens of infected tissue. Finding an organism in a tissue sample depends on the parasitic burden, the efficacy of the host's immune response, any coexisting contamination of the ulcer, and the age of the lesion (Findings in old lesions are frequently non-diagnostic.). The parasites consist of a nucleus and a kinetoplast surrounded by a cell wall. Visualization of all 3 features (nucleus, cell membrane, and kinetoplast) is required to make the diagnosis microscopically.

Direct visualization of the organism is diagnostic but can be difficult because of its small size (2-4 mm) and because of subtle distinguishing characteristics on routine hematoxylin-eosin stains. Identification often requires an experienced pathologist and lengthy searches by using high magnification, particularly when organisms are sparse. Giemsa, Brown-Hopps, Gram, or Leishman stains may enhance *Leishmania* organisms on touch preparations, tissue aspiration, or biopsy samples. The diagnostic sensitivity of microscopic identification of leishmanial amastigotes is typically 75-85% but may vary widely, depending on the size of the inoculum

and observer's experience. The ideal way to microscopically identify the parasite is with direct touch preparations from the lesion or biopsy tissue stained with Giemsa rather than with routine tissue sections.

The polymerase chain reaction (PCR) is now routinely used in experienced laboratories as a rapid diagnostic technique. Even in remote locations and under harsh conditions, this technique has proven its worth, as evidenced by the U.S. military's recent experience with leishmania in Iraq. Validated genus-specific PCR primers exist, and approval of this assay by the U.S. Food and Drug Administration (FDA) is being sought so it can be used in worldwide facilities certified by the College of American Pathologists (CAP). Species-specific PCR probes allow for rapid speciation in confirmed cases of leishmania and are undergoing final validation. FDA approval of these assays might also be sought, but cases can be referred to reference labs in the United States for rapid diagnosis and speciation.

In vitro cultures of tissue are regularly obtained to aid in diagnosis and to identify *Leishmania* species. This technique has approximately the same diagnostic sensitivity as that of pathologic evaluation, but special laboratory capabilities and technical skills are required. These are currently available in only 2 reference laboratories in the United States (at the Centers for Disease Control and Prevention [CDC] and the Walter Reed Army Institute of Research). The value of this method is that the species of the parasite can be identified on the basis of long-standardized isoenzyme patterns on cellulose acetate electrophoresis after the parasite is grown in vitro.

In vivo diagnosis of *Leishmania* organisms can also be achieved by inoculating clinical specimens into golden hamsters or certain highly susceptible mouse strains. Although results are not available for weeks to months, they are useful in diagnosing the disease, especially in difficult cases.

***Mucocutaneous or VL***: aspirates or touch preparations of mucosal or visceral tissue dermal scrapings may be processed like cutaneous samples are, as described above.

***Systemic leishmaniasis:*** a variety of immunodiagnostic serologic tests have been developed to aid in the diagnosis of systemic leishmaniasis. The only serologic tests are limited to species of *Leishmania* that cause visceral disease. Limitations include false-negative serologic results due to inadequate titers of antibodies late in the course of the disease and false-positive results in the setting of other infectious or autoimmune diseases.

The most promising serologic test to date is an *L. chagasi* recombinant amastigotes K39 (rK39)–based antigen test system that has been used with enzyme-linked immunosorbent assay (ELISA), a direct agglutination test (DAT), and even a nitrocellulose dipstick test. The degree of conservation of the K39 gene is high among isolates of the *L. donovani* family, including *L. chagasi* and *L. infantum.* Therefore, this test is useful for most recognized cases of visceral leishmania. Assays based on rK39 antigen are highly sensitive and specific and validated in several large studies worldwide.

Ancillary tests important in the diagnosis of visceral leishmania include determinations of the CBC count with differential; liver function tests; and lipase, amylase, gamma globulin, and albumin tests.

**Other Tests.** Skin testing: similar to the purified protein derivative (PPD) test, the Montenegro LST has been used for decades to determine previous or current exposure to *Leishmania* parasites. LST is not used to distinguish between active and resolved disease, but can be useful in evaluating known naive populations that become immunologically responsive to leishmanial antigens. LST is not applicable to immunologically anergic patients with widely disseminated cutaneous disease. Because LST is not standardized, the FDA has not approved it; therefore, LST is not available as a diagnostic tool in the United States.

Parasite speciation: cellulose acetate electrophoresis is a well-standardized method for determining the species of parasites grown from clinical samples. Although this test is standardized, it requires experience and special facilities, and therefore, it is available only in highly specialized diagnostic facilities.

**Procedures.**Perform biopsy and obtain dermal scrapings and needle aspirates. Obtain bone marrow or splenic aspirates and analyze them for visceral disease.

**Histologic Findings.**LCL is characterized by irregular acanthosis, with or without epidermal ulceration, and dense dermal infiltrate of mixed inflammatory cells, particularly plasma cells, lymphocytes, and histiocytes. Early in the course of localized disease, organisms may be numerous and found readily in the cytoplasm of macrophages. As the lesion ages and as delayed-type immunity is up-regulated, the infiltrate is replaced by noncaseating granulomata in which few or no organisms can be seen. Ulcerated lesions are often secondarily infected by bacteria, in which case histologic changes may be non-specific. Results with biopsy specimens obtained from old (>6 months), partially treated, or low-burden infections are frequently non-diagnostic.

DCL occurs in individuals with poor cellular immunity to *Leishmania* parasites. Histologic diagnosis is straightforward in these cases. The dermis contains sheets of macrophages containing great numbers of amastigotes, with few lymphocytes or plasma cells.

PKADL has a variable histology that is determined by the degree of host immunity and the parasite load. Granulomatous histology is seen with low numbers of organisms, whereas diffuse histiocytic or xanthomatous infiltrates may be seen with numerous organisms.

RCL is usually difficult to confirm because of the rarity of organisms and because of its histologic similarity to lupus vulgaris.

Aspirates from bone marrow, lymph nodes, or the spleen are typically obtained to make a histologic diagnosis of kala azar. As with diagnosis with skin samples, diagnosis based on these aspirates depends on identification of *Leishmania* parasites, which are usually plentiful in macrophages.

**Medical Care.**Tailor treatment to the individual because leishmaniasis is caused by many species or subspecies of the *Leishmania* protozoa, all of which have different degrees of virulence and clinical predilections. Consider the clinical

pattern of disease, the geographic region in which the infection occurs, the immunologic status of the patient, and the previous attempts at treatment when therapy is started.

Although treatment used to be the recommendation for every case of leishmania after the infection is identified, this is no longer the conventional practice. Treatment must be a balance of risk versus benefit, especially in the case of *L major,* which is generally a self-limited cutaneous illness that heals within 12 months. For lesions caused by this species, treatment is not generally necessary unless the lesion is in a cosmetically or functionally sensitive site. Cases due to *L. tropica,* another Old World species, may have a more chronic course (up to years); this organism has been implicated in occasional cases of recidivans or viscerotropic leishmaniasis. As such, treatment may need to be more prudent in cases caused by this species.

With New World leishmaniasis, as many as 10% of untreated individuals may have recurrences in the form of chronic ulcers, recidivans lesions, or mucocutaneous involvement. Multiple treatment options are used throughout the world. In addition to parenteral and oral medications, local therapies for some forms of cutaneous leishmaniasis include the following: cryotherapy; infiltration of sodium stibogluconate 0.3-0.8 mL; intralesional heat therapy with 40-42°C for 12 hours; and various topical paromomycin preparations, typically 15% with 10% urea.

Surgical excision is usually not recommended because of the risk of relapse and cosmetic disfigurement. In some areas of the world (Russia, the Middle East), live attenuated *L. major* promastigotes have been used preemptively to immunize against Old World cutaneous leishmaniasis. This practice produces a modified form of the disease and results in a scar at the injection site. Immunity to subsequent *L. major* infections usually is good; however, as with natural infection, cross-reactive immunity to other *Leishmania* species does not occur. Many more universally useful and cosmetically acceptable *Leishmania* vaccine formulations are under investigation. To date, no vaccines are commercially available.

Treat malnutrition, concurrent systemic illness (e.g. HIV disease, tuberculosis), or local infection (secondary bacterial) accordingly. Despite successful therapy, whether the parasites are completely eradicated is unclear because reactivation of leishmaniasis with immunosuppression has been reported.

For 50 years, the mainstay of antileishmanial therapy has been pentavalent antimony (sodium stibogluconate or meglumine antimonate). These drugs are not marketed in the United States, but they may be obtained through the CDC under an investigational new drug application. Cure rates are 90-97% with 1-3 treatment courses; however, the drawbacks are considerable. These drugs are expensive and difficult to obtain. They must be delivered parenterally, they have numerous adverse effects, they may have lot-to-lot variability, and they are becoming increasingly less effective because of the emergence of drug-resistant parasites.

Alternative treatment regimens with acceptable cure rates are pentamidine, paromomycin, interferon-gamma plus antimony, and amphotericin B (and less

toxic variations, e.g. liposomal amphotericin B, amphotericin B lipid complex, and amphotericin B colloidal dispersion).
**Prevention:** leishmaniasis is preventable by avoiding contact with the vector. The sandfly is most active from dawn to dusk, it is small enough to fit through standard mosquito netting, it makes no audible noise, and it is a relatively poor flyer.Effective prevention may be achieved by avoiding nighttime outdoor activities, by using topical insecticides (e.g. diethyltoluamide [DEET]) on exposed skin surfaces, by using insecticide-impregnated clothing (permethrin stays in or on the material for many washings), by using fine mesh mosquito netting treated with permethrin, and by sleeping with a fan on.
Protective immunity after medical treatment or infection is 97-98% effective against disease caused by the same species of *Leishmania.* Deliberate scarification of the extremities with material from human lesions was once practiced to prevent scarring that may result from a later natural infection of the face.
The treatment of infected persons and elimination of diseased reservoir vertebrates can reduce the source of infections.
**Prognosis.**In well-nourished individuals with intact immune systems, recovery is expected after treatment with the appropriate medication.
**Patient Education.**Behavior modification to avoid vector contact, combined with insect control measures, significantly diminishes the risk of acquiring infection.

## 12.3. Pediculosis

**Background:** Pediculosis (i.e. louse infestation) dates back to prehistory. The oldest known louse eggs (i.e. nits) are aged approximately 10,000 years (i.e. fossils, not viable). Lice are so ubiquitous that terms and phrases such as "lousy," "nit-picking," and "going over things with a fine-tooth comb" are part of everyday vocabulary.
Over the last 3 decades, the incidence of pediculosis has risen steadily, making the diagnosis and treatment of louse infestation one of the most common tasks in general medical practice. This article focuses on the pathophysiology and life cycle of 3 prevalent human ectoparasites, (1) *Pediculus humanus capitis* (i.e. head louse), (2) *Pediculus humanus corporis* (i.e. body louse), and (3) *Phthirus pubis* (i.e. pubic louse). The clinical aspects of presentation, diagnosis, and treatment of these ancient and common human pests are also discussed.
**Pathophysiology:** Human lice (*P. humanus* and *P. pubis*) are found in all countries and climates. They belong to the order Anoplura, the sucking lice, and are classified as insects. Mammals are the hosts for all Anoplura, and, although lice prefer human hosts, *P. humanus* is also known to live and reproduce on pigs.
The Anoplura are wingless and have 3 pairs of legs, each ending with a clawlike talus for grasping. The size and shape of the claws are adapted to the texture and shape of the hairs and/or clothing fibers they grasp. Their bodies are flat and covered with tough chitin. Human lice have small anterior mouthparts with 6

hooklets that aid their attachment to human skin during feeding. The sucking mouthparts retract into the head when the lice are not feeding. In general, lice feed approximately 5 times per day for approximately 35-45 minutes each time.

In each species, the female louse is slightly larger than her male counterpart. The life cycle of lice is 30-35 days from egg to adult. Early death is common, resulting from gut rupture during feeding or cementing of the female to the hair shaft during ovipositioning.

***P. humanus capitis***. The average length of the head louse is 1-2 mm. The louse is white to gray and has a long, dorsoventrally flattened, segmented abdomen. The average life span is 30 days. After incubation of the ova (8-10 d), the nymph molts 3 times before reaching its adult form (8-10 d later). The female head louse lays as many as 10 eggs per 24 hours, usually at night. She positions her ova at the base of the hair shaft, close to the scalp, with a predilection for the posterior hairline and postauricular areas. The female louse cannot survive for more than 1 day off the human head.

***P. humanus corporis***. The body louse is larger than the head louse. Body lice range in size from 2-4 mm; the female lice are larger than the male lice. The body louse is also flat and white to gray with a segmented abdomen. Unlike the head louse and the pubic louse, the body louse does not live on the human body. *P. humanus corporis* lives in human clothing, crawling onto the body only to feed, which predominantly occurs at night. *P. humanus corporis* prefers cooler temperatures, living and laying its 10-15 eggs per day some distance from the human body on the fibers of clothing, mainly close to the seams. The adult female body louse, unlike the head louse, can survive as long as 10 days away from the human body without a blood meal. The life cycle from nit to death is approximately 35 days, with 3 episodes of molting before maturity.

***P. pubis***. The pubic louse gets the nickname of "crab" from its shorter, broader body (0.8-1.2 mm) and large front claws, which give it a crablike appearance. The pubic louse is white to gray, oval, and has a smaller abdomen than the other 2 forms. The average life cycle is also 35 days, although the period from ova to adult (15 d) is slightly longer than that of the other 2 forms. The average female pubic louse lays only 1-2 eggs per day. Their large claws enable pubic lice to grasp the coarser pubic hairs in the groin, perianal, and axillary areas. Heavy infestation with *P pubis* can also involve the eyelashes, eyebrows, facial hair, and, occasionally, the periphery of the scalp. These insects are less mobile than *P. humanus* and *P. corporis,* mainly resting while attached to human hairs. They cannot survive off the human host for more than 1 day.

**Nits**. The average nit (i.e. ovum) of the 3 types of lice is 0.8 mm long. The nit attaches to the base of the hair shaft or to fibers of clothing with strong, highly insoluble cement. The nit is topped with a tough but porous cap known as the operculum. This porous sheath allows for gas exchange while the nymph develops in the casing. The ova require optimum conditions of 30°C and 70% humidity to hatch within the average time frame of 8-10 days; however, the incubation period is longer at lower temperatures. Ova do not hatch at temperatures lower than 22°C

but can remain alive for as long as 1 month away from the body (i.e. on fomites, clothing, brushes).

**Frequency.** Pediculosis is extremely common; an estimated 10-12 million Americans, a quarter of whom are elementary school children, are infested. Hundreds of millions of cases of louse infestation are reported annually worldwide, with an apparent increase over the past few decades.

**Mortality/Morbidity.** Mortality with pediculosis occurs from the 3 infectious vector-borne diseases (i.e. typhus, relapsing fever, trench fever) that are carried by *P. corporis*. The morbidity associated with pediculosis no doubt relates to the social stigma attached to any of the 3 types of infestation. Pruritus, bite reactions, and secondary skin infections can also cause significant morbidity.

**Sex.** Girls are at higher risk of head louse infestation than boys because of social behavior (e.g. social acceptance of close physical contact; sharing of hats, combs, hair ties). No sexual predilection exists in body or pubic louse infestation; males and females are equally likely to become infested.

**Age.** In head louse infestation, children aged 3-11 years are most likely to become infested because of close contact in classrooms and daycare facilities. Age is not a significant risk factor in body louse infestation. *P. pubis* infestation occurs more frequently in people aged 14-40 years who are sexually active.

**Causes.** Causative organisms include *P. humanus capitis* (head louse), *P. humanus corporis* (body louse), and *P. pubis* (pubic louse).

Risk factors for infestation with *P. humanus capitis*.Factors predisposing patients to head louse infestation include young age, close crowded living conditions, sex, race, and warm weather. The risk of nosocomial transmission is low, unless close patient-to-patient contact (e.g. playrooms, institutions) is present.Based on an 11-year study of the Israel Defense Force, the head lice infestation rate is highest during the warmer summer months.

Risk factors for infestation with *P. humanus corporis*. The risk factors for body louse infestation include the presence of close, crowded living situations (e.g. crowded buses and trains).Social circumstances in which the washing and/or changing of clothing is not possible are also significant risk factors for body lice.

*P. corporis* can also be acquired through the use of bedding or clothing recently used by an individual with lice; thus, those individuals at high risk for infestation are those who are homeless, those who are impoverished, and people living in refugee camps.

Risk factors for infestation with *P. pubis*. Risk factors for infestation of the pubic louse also include crowded living conditions.Intimate or sexual contact with an infested individual is another common risk factor.Because these organisms most often are spread through close or intimate contact, *P. pubis* infestation is classified as a sexually transmitted disease (STD). Condom use does not prevent transmission of *P pubis*. Upon diagnosis of pubic lice, concern should be raised about the possibility of concomitant STDs.

In children, infestation usually is contracted from a parent who is infested and rarely is sexually transmitted. In most cases of child infestations, transmission is due to shared bed linens and close nonsexual contact.

**History.**Infestations are underreported because of the social stigma attached, namely the preconceived notion that lice of any kind are related to dirt and/or poor personal hygiene.

*P. humanus capitis*. In head louse infestations, parents often seek assessment for their school-aged children after becoming aware of an outbreak at school.Pruritus is the major complaint, and parents may note the lice and nits in the hair of the child.The length of time the problem has been present is often valuable information because most children are infested with head lice for as long as 2 months before their discovery.Areas affected in head louse infestation include the scalp, the back of the neck, and postauricular areas.

*P. humanus corporis*.Patients infested with *P. corporis* (generally people of low socioeconomic status) complain of nocturnal pruritus, particularly in the axillary, truncal, and groin regions. The lice move from the clothing to the body at nighttime to feed, causing intense pruritus.The investigating physician should inquire about the patient's socioeconomic status and living conditions.

*P. pubis*. With pubic louse infestation, involvement with pruritus of the groin, axillae, and eyelashes or eyebrows can help to discern *P. pubis* infestation from head or body louse infestation.Adults infested with *P. pubis* are usually sexually active and have groin and body hair involvement.Children have eyelash and eyebrow involvement. Parents of children infested with *P. pubis* should be questioned about being infested because the parents are usually the source of infestation.Patients may describe associated features such as papules or wheals, indicating bite reactions. Patients may have a history of secondary infection after excoriation, which may help to confirm the presence of an infestation.

A diagnosis of any type of pediculosis requires the finding of live specimens of lice and/or a viable nit (i.e. one located at the base of the hair shaft <2 mm from the scalp). The practitioner should assess the patient's risk factors for infestation (e.g. age, sex, race, social and/or economic status, crowded environment).

**Physical.***P. humanus capitis*.Patients infested with head lice generally present with an itchy scalp. The back of the neck and postauricular areas are commonly involved.Excoriations may be present, and, if so, secondary infection, (i.e. impetigo) should be excluded and, if present, treated.In patients infested with head lice, lymphadenopathy in the posterior auricular and cervical nodes is not uncommon.Bite reactions manifested as pruritic papules and/or wheals may be present, depending on the length of time since the blood meal. Healed bites may reappear when new bites occur in other areas.Close inspection of the scalp in affected patients may reveal the nits, live lice, and small, dark specks of insect feces. True nits can be differentiated from dried hairspray and hair casts by attempting to separate the nit from the hair; the hair casts and dried hairspray separate easily, while nits remain securely attached. If the physician remains unsure, a Wood lamp examination reveals yellow and/or green fluorescence of the

lice and their nits.Uncommonly, in patients who are heavily infested and untreated, the hair can become tangled with exudates, predisposing the area to fungal infection. This results in a malodorous mass known as a plica polonica. Numerous lice and nits are found under the matted hair mass.

*P. humanus corporis*. Physical examination findings in body louse infestation include multiple erythematous papules (bites) located anywhere on the body but concentrated in the axillae, groin, and trunk (i.e. those areas most often covered by clothing). Thus, the face, feet, and arms are often not affected.Maculae cerulea may be present as blue-gray macules, which are actually a discoloration of the skin due to the insect's bite. Enzymes in the louse saliva are believed to cause the breakdown of human bilirubin to biliverdin, causing the change in skin color associated with maculae cerulea. The finding of maculae cerulea is believed to be pathognomonic for infestation with lice.The development of secondary infections due to excoriations is also possible. The diagnosis of body lice depends on the close examination of the patient's clothing for lice, nits, and insect feces. The seams of clothing worn on the axillae and groin regions are common sites of residence. The number of body lice per host is usually approximately 10, although as many as 1000 lice can be present.Body louse infestation is also known as vagabond disease, and patients that have infestation for many years can develop a condition termed vagabond skin. The skin becomes thickened and darkened after years of bites and subsequent rubbing and excoriations.Individuals with *P. corporis* infestation should also be examined for the presence of pubic and head lice. Examining the individual for systemic illness that may be related to one of the vector-borne diseases associated with *P. corporis* is also important.

*P. pubis*. The primary complaint of patients with pubic lice is pruritus in the affected areas. Another clinical feature of pubic louse infestation is the presence of pathognomonic maculae cerulea.The groin, axillae, eyebrows, eyelashes and, rarely, facial hair, may be sites of infestation. Scalp involvement is rare and is usually confined to the marginal areas. In adults, eyelash involvement in the absence of genital involvement is rare. Excoriations are common. Because of the less-mobile nature of pubic lice, they are more likely to be found on affected areas clasping onto the hairs near the skin's surface.Inguinal or axillary lymphadenopathy has also been reported with pubic louse infestation.

**Lab Studies.** A Wood lamp examination of the area considered to be infested shows yellow-green fluorescence of lice and nits.Because the diagnosis of infestation requires identification of a live louse and/or a viable nit, examining suggestive particles under the microscope confirms the diagnosis.A fine-tooth "bug-busting" comb is useful to dislodge eggs and to remove live lice/nymphs. Cellulose tape can be applied over an infested area to pick up lice and place them on a microscopic slide to be examined.

Scrapings for a fungal culture can be taken if dermatophyte infection is a differential diagnosis. This is useful when the diagnosis is unclear, i.e. no nits or lice have been identified.

In *P. pubis* infestation, blood tests and a thorough examination for concomitant STDs, including HIV infection, are appropriate if the physician considers the individual to be at risk for these conditions.

**Histologic Findings.**Histology is rarely required to make a diagnosis. Examination of a bite shows intradermal hemorrhage and a deep, wedge-shaped infiltrate with many eosinophils and lymphocytes.

**Medical Care.**

*P. humanus* corporis. Treatment of *P. humanus corporis* with any pediculicide is usually unnecessary because the louse lives on the clothing. Treatment of clothing and bed linens includes washing in hot water and drying with high heat. Dry cleaning is also effective for killing lice and their nits on clothing. Education about hygiene and accessibility to laundering facilities are important in preventing the spread of body lice and reinfestation. In cases of heavy pediculosis, treatment of the body with a pediculicide shampoo or lotion may be beneficial, especially if coexistent head or pubic louse infestation may be present.

*P. humanus capitis* and *P. pubis*. Pediculicides: These include permethrin, lindane, malathion, or mercuric oxide ointment. The pyrethroids are neurotoxic to lice; however, they are not very effective against developing nits, although they do have a residual effect. Lotions appear to be more efficacious than shampoos because of their increased contact time with the skin and hair of affected areas. Permethrin is available as a 1% solution (Nix) and as a 5% solution (Elimite), and a formulation of pyrethrin and piperonyl butoxide (Rid) is available. Permethrins are usually the first line of treatment, although resistance to permethrin is an increasingly important problem. Lindane (hexachlorocyclohexane, a chlorinated hydrocarbon) is in the same pharmacologic class as dichlorodiphenyl trichloroethane (DDT). The use of lindane is controversial because of its known CNS toxicity. The compound is extremely lipid-soluble and, therefore, is highly permeable to the CNS. Acute lindane poisoning has been reported after ingestion of amounts as small as 5 mL or 50 mg. Kwell (lindane shampoo) has been removed from the Canadian market because of the availability of safer alternatives. Malathion (Ovide) is an irreversible acetylcholinesterase inhibitor that is specific for insects. The US Food and Drug Administration (FDA) recently approved malathion for use against head lice in the United States. Malathion is available as a 0.5% and a 1% solution. Mercuric oxide ointment is useful in the treatment of eyelash infestation with *P pubis*. Asphyxiants: petrolatum is often used, with good results, for eyelash infestation. The petrolatum covers the lice and their nits, preventing respiration. The dead lice are removed mechanically, usually with tweezers.

Specific oral antibiotics: Co-trimoxazole (i.e. trimethoprim and sulfamethoxazole) and ivermectin have been found to be effective against head louse infestation when taken orally.

Mechanical removal and shaving. Solvents that help to dissolve the cement away from the nit aid in mechanical removal of nits with fine-tooth combs (e.g. LiceMeister). Formic acid and plain white vinegar have been shown to be effective solvents. In most studies that compare mechanical removal (i.e. wet-combing q2-

3d for a minimum of 2 weeks) with a pediculicide, mechanical removal alone is not as effective.
Shaving is effective but is usually not necessary or socially acceptable. However, in resistant disease, it may be a consideration.
**Prevention.** Environmental eradication. Fomites (e.g. pillow cases, linens, towels, toys, hats) should be washed in hot water and dried. Fomites should be exposed to temperatures exceeding 55°C for at least 5 minutes. Any object that the infested child or parent has come into contact with should be washed thoroughly in hot water.Another way to administer environmental control is to seal potential fomites in plastic bags for at least 2 weeks so that all the nits hatch and die without a blood meal.Providing education to children about the sharing of hats, combs, and hair-ties is also a good idea.Giving children separate areas to store their belongings in the classroom may help prevent the spread of lice. Treatment of contacts. The treatment of family members, friends, and/or other close contacts is very important in helping to prevent further spread of lice and in preventing reinfestation.Patient education regarding treatment of contacts is essential. Parents with children who are infested should be advised to treat the entire family with a pediculicide and to provide environmental fomite control.Education about hygiene and accessibility to laundering facilities are important in preventing the spread of body lice and reinfestation.
**Patient Education.**Education is important with respect to the proper use of the chosen pediculicide, nit removal, and environmental control.In cases of school-wide head louse infestations, all children and their family members should be examined for infestation. The preconceived notion that head lice are related to dirt and poor personal hygiene should be dispelled.

# XIII. VIRAL INFECTIONS

## 13.1.Herpes Simplex

**Synonyms and related keywords:** HSV, herpes genitalis, genital herpes, herpes labialis, orolabial herpes, HSV-1, HSV type 1, herpes simplex virus type 1, HSV-2, HSV type 2, herpes simplex virus type 2, localized eczema herpeticum, disseminated eczema herpeticum, Kaposi's varicelliform eruption.

**Background.**Herpes simplex viruses (HSVs) are DNA viruses that cause acute skin infections and present as grouped vesicles on an erythematous base. Rarely, these viruses can cause serious illness and can affect pregnancy, leading to significant harm to the fetus. Most infections are recurrent and tend to reappear at or near the same location. Herpes labialis is the most common infection caused by HSV type 1 (HSV-1), whereas genital herpes is usually caused by HSV type 2 (HSV-2). Other clinical manifestations of HSV infection are less common.

**Pathophysiology.**Intimate contact between a susceptible person (no preantibodies) and an individual who is actively shedding the virus is required for HSV infection to occur. Contact must involve mucous membranes or open or abraded skin. HSV invades and replicates in neurons as well as in epidermal and dermal cells. Virions travel from the initial site of infection to the sensory dorsal root ganglion, where latency is established. Viral replication in the sensory ganglia leads to recurrent clinical outbreaks. These outbreaks can be induced by various stimuli, such as trauma, ultraviolet radiation, extremes in temperature, stress, immunosuppression, or hormonal fluctuations. Viral shedding, leading to possible transmission, occurs during primary infection, during subsequent recurrences, and during periods of asymptomatic viral shedding.

**Causes.** HSV-1 and HSV-2 are the causative agents of herpes genitalis, herpes labialis, herpes gladiatorum, herpes whitlow, herpetic keratoconjunctivitis, eczema herpeticum, herpes folliculitis, lumbosacral herpes, disseminated herpes, neonatal herpes, and herpes encephalitis. They have also been linked to some cases of erythema multiforme. A febrile illness, exposure to ultraviolet light, trauma, upper respiratory infection, or emotional stress may trigger recurrent herpes labialis due to HSV-1.

The patient's geographical location, socioeconomic status, and age influence the frequency of HSV-1 infections. The highest prevalence of antibodies to HSV-2 occurs in female prostitutes and male homosexuals.

**Frequency.**Internationally, serologic evidence of HSV-1 infection by early adulthood is near 70-80%. HSV-2 seroprevalence has been reported to be as high as 40% worldwide. More than one third of the world's population has recurrent clinical HSV infections.

**Mortality/Morbidity.**Severe complications may be associated with herpes simplex. This is especially true in females who are pregnant and in individuals

with immunosuppression who may develop disseminated infection and encephalitis. The most common complication of primary HSV-2 genital infection is bacterial superinfection. In women, systemic complications, such as urinary retention and aseptic meningitis (seen in up to 25% of women), can occur. The associated pain, paresthesia, and discomfort, as well as the psychosocial impact, of herpes simplex outbreaks cause significant morbidity to the individuals who are affected.

Individuals co-infected with HSV and HIV and who have herpetic mucosal lesions are more likely to transmit HIV during sexual contact. Organ transplant recipients and patients with HIV/AIDS may develop herpetic lesions that exhibit an unusual morphology. Moreover, patients with Darier disease, severe atopic dermatitis, and mycosis fungoides may develop life-threatening disseminated Kaposi varicelliform eruption.

Another serious consequence of HSV is the transmission of the virus to a neonate by a mother who is infected. Asymptomatic maternal shedding occurs approximately 7% of the time and is responsible for most neonatal HSV infections. HSV infections in neonates are most commonly due to HSV-2 and most are acquired peripartum, although in utero and postpartum transmission also occur. Transmission is estimated to occur at a rate of 1 case in 3500-5000 deliveries in the United States. Neonatal infection can cause long-term sequelae and rarely death.

**Sex.**The frequency of HSV-1 and HSV-2 antibodies is slightly higher in females than in males. However, women are more likely than men to be protected from genital HSV infection by the use of barrier methods.

**Age.**The frequency of HSV-1 infection in children varies with the socioeconomic status. Approximately, one third of children from lower socioeconomic families exhibit some evidence of HSV-1 infection by age 5 years. The frequency increases to 70-80% by early adolescence/adulthood. In contrast, only 20% of children from middle-class families seroconvert. The frequency of infection remains fairly stable until the second to third decade of life when it increases to 40-60%. The rate of HSV-2 seroconversion is highest in sexually active young adults.

**History.**Primary infection with HSVs is clinically more severe than recurrent outbreaks. However, most primary HSV-1 and HSV-2 infections are subclinical and may never be clinically diagnosed.

***Orolabial herpes***. Herpes labialis (e.g. cold sores, fever blisters) is most commonly associated with HSV-1 infection. Oral lesions caused by HSV-2 have been identified, usually secondary to orogenital contact. Primary HSV-1 infection often occurs in childhood and is usually asymptomatic.

Primary infection: symptoms of primary herpes labialis may include a prodrome of fever, followed by a sore throat and mouth and submandibular or cervical lymphadenopathy. In children, gingivostomatitis and odynophagia are also observed. Painful vesicles develop on the lips, the gingiva, the palate, or the tongue and are often associated with erythema and edema. The lesions ulcerate and heal after 2-3 weeks.

Recurrences: the disease remains dormant for a variable amount of time. Pain, burning, itching, or paresthesia usually precedes recurrent vesicular lesions that eventually ulcerate or form a crust. The lesions most commonly occur in the vermillion border, and symptoms of untreated recurrences last approximately 1 week.

***Genital herpes***: HSV-2 is identified as the most common cause of herpes genitalis. However, HSV-1 has been increasingly identified as the causative agent in as many as 30% of cases of primary genital herpes infections likely secondary to orogenital contact. Recurrent genital herpes infections are almost exclusively caused by HSV-2.

Primary infection: primary herpes genitalis occurs within 2 days to 2 weeks after exposure to the virus and has the most severe clinical manifestations. Symptoms of the primary episode typically last 2-3 weeks.

In men, painful, erythematous, vesicular lesions that ulcerate most commonly occur on the penis, but they can also occur on the anus and the perineum. In women, primary herpes genitalis presents as vesicular/ulcerated lesions on the cervix and as painful vesicles on the external genitalia bilaterally. They can also occur on the vagina; the perineum; the buttocks; and, at times, the legs in a sacral nerve distribution. Associated symptoms include fever, malaise, edema, inguinal lymphadenopathy, dysuria, and vaginal or penile discharge.

Females may also have lumbosacral reticulopathy, and as many as 25% of women with primary HSV-2 infections may have associated aseptic meningitis.

Recurrences: after primary infection, the virus may be latent for months to years until a recurrence is triggered. Recurrent clinical outbreaks are milder and often preceded by a prodrome of pain, itching, tingling, burning, or paresthesia.

Individuals who are exposed to HSV and have asymptomatic primary infections may experience an initial clinical episode of genital herpes months to years after becoming infected. Such an episode is not as severe as a true primary outbreak.

More than one half of individuals who are HSV-2 seropositive do not experience clinically apparent outbreaks. However, these individuals still have episodes of viral shedding and can transmit the virus to their sexual partners.

***Other HSV infections***

Localized or disseminated eczema herpeticum is also known as Kaposi varicelliform eruption. Caused by HSV-1, eczema herpeticum is a variant of HSV infection that commonly develops in patients with atopic dermatitis, burns, or other inflammatory skin conditions. Children are most commonly affected.

Herpes whitlow, vesicular outbreaks on the hands and the digits, was most commonly due to infection with HSV-1. It usually occurred in children who sucked their thumbs and, prior to the widespread use of gloves, in dental and medical health care workers. The occurrence of herpes whitlow due to HSV-2 is increasingly recognized, probably due to digital-genital contact.

Herpes gladiatorum is caused by HSV-1 and is seen as papular or vesicular eruptions on the torsos of athletes in sports involving close physical contact (classically wrestling).

Disseminated HSV infection can occur in females who are pregnant and in individuals who are immunocompromised. These patients may present with atypical signs and symptoms of HSV, and the condition may be difficult to diagnose.

Neonatal HSV. HSV-2 infection in pregnancy can have devastating effects on the fetus. Neonatal HSV usually manifests within the first 2 weeks of life and clinically ranges from localized skin, mucosal, or eye infections to encephalitis, pneumonitis, disseminated infection, and demise. Factors that increase the risk of transmission from mother to baby include the type of genital infection at the time of delivery (higher risk with active primary infection), prolonged rupture of membranes, vaginal delivery, and an absence of transplacental antibodies. The mortality rate is extremely high (>80%) if untreated.

Herpetic sycosis, a follicular infection with HSV, may present as a vesiculopustular eruption on the beard area. This infection often results from autoinoculation after shaving through a recurrent herpetic outbreak.

**Physical.**Clinical HSV infections appear as clustered vesicles on an erythematous base. They often progress to pustular or ulcerated lesions, and they eventually form a crust. HSV lesions tend to recur at or near the same location within the distribution of a sensory nerve. Systemic symptoms, such as fever, malaise, and acute toxicity, may accompany the lesions, especially in primary infections. Each condition has associated symptoms and clinical findings (see History above).

Although HSV infections may occur anywhere on the body, 70-90% of HSV-1 infections occur above the waist. In contrast, 70-90% of HSV-2 infections occur below the waist.

Physical manifestations of HSV infections in patients who are immunocompromised are usually similar to those in healthy patients. However, larger lesions or necrotizing ulcers may occur, and widespread areas may be involved.

Neonatal HSV may be difficult to diagnose because, often, no mucocutaneous lesions are present on physical examination. Respiratory distress, jaundice, and seizures may occur.

**Complications.** The most common complication of HSV infections is bacterial superinfection. In women with primary HSV-2 infection, aseptic meningitis is also common.Significant complications, such as visceral and CNS dissemination and long-term sequelae, are rare and occur in patients who are immunocompromised or in cases of neonatal HSV.Patients with AIDS who are treated with intravenous acyclovir may develop thymidine kinase–negative strains of HSV that are resistant to acyclovir. These patients may be successfully treated with intravenous foscarnet or topical cidofovir.Babies born to mothers with genital HSV infection should be closely monitored for any signs of infection and promptly treated if signs of the disease develop. Neonatal HSV infection has a mortality rate of more than 80% if untreated and a mortality/significant morbidity rate of approximately 50% even when treated.

**Lab Studies.**Detection and typing of HSV can be completed by obtaining a viral culture from skin vesicles. Early in the course of recurrent infection, 80-90% of viral cultures of untreated lesions are positive, but the false-negative rate increases after 48 hours of lesion onset.

HSV DNA detection is performed in specific instances by polymerase chain reaction (PCR).

The virus may be isolated from cerebrospinal fluid (CSF) (in newborns), stool, urine, throat, anogenital mucosa, nasopharynx, and conjunctivae.

In the office, a Tzanck smear can be performed as a rapid test for the presence of multinucleated giant cells, though the findings are not specific for the type of herpes virus. A Tzanck smear is prepared by scraping the floor of the herpetic vesicle; samples may be stained with either a Wright stain or a Papanicolaou stain. Approximately 50% of the results are positive.

Direct fluorescent antibody testing may be used on air-dried smears, and approximately 75% of the results are positive.

Serologic assays may be useful in identifying organ transplant recipients or pregnant women who may be at risk for HSV reactivation. Their use is also becoming more common for confirming infection and for testing of partners or those with asymptomatic infection.

Enzyme-linked immunosorbent assays (ELISAs) and several other HSV-1 and HSV-2 serologic assays that can detect antibodies against these viruses are available.

A rapid HSV-2 POCKit test is now commercially available and has a high sensitivity. Western blot assays are highly sensitive and specific, but they are only available for research purposes.

Immunoperoxidase techniques may be used to distinguish HSV-1 and HSV-2 antigens in formalin-fixed tissue samples.

**Histologic Findings.**Cells infected with HSV demonstrate ballooning and reticular epidermal degeneration, acanthosis, and intraepidermal vesicles. Intranuclear inclusion bodies, multinucleate giant keratinocytes, and multilocular vesicles may also be present.

**Medical Care.** Most HSV infections are self-limited. However, antiviral therapy shortens the course of the symptoms and may prevent dissemination and transmission.Intravenous, oral, and topical antiviral medications are available for treatment of HSV and are most effective if used at the onset of symptoms. Oral therapy can be given at the time of the episode or as chronic suppressive therapy.Treatment of herpes labialis and herpes genitalis generally consists of episodic courses of oral acyclovir and prodrugs valacyclovir and famciclovir. Oral antiviral medications, acyclovir, valacyclovir, and famciclovir, may be used (off label) as therapy for other uncomplicated HSV conditions (e.g. herpes whitlow), and the same doses as those used for herpes genitalis treatment are commonly recommended.Commercially available topical treatments for herpes are much less effective than oral therapy. Complicated HSV infections, cutaneous and/or visceral

dissemination, neonatal HSV, and severe infections in those who are immunocompromised should promptly be treated with intravenous acyclovir.
In patients who are immunocompromised and have recurrent HSV infections, acyclovir-resistant HSV strains have been identified, and treatment with intravenous foscarnet or cidofovir may be used.
**Activity.**Avoidance of known triggers of HSV recurrences, such as UV light and smoking, may diminish the number of outbreaks experienced by an individual.
**Prevention.** HSV viral shedding is greatest during clinically evident outbreaks; however, transmission from individuals who are seropositive to their partners who are seronegative usually occurs during asymptomatic HSV shedding periods. Therefore, preventing transmission requires more than abstaining from intimate contact during outbreaks.Barrier methods, such as condoms, only confer 10-15% protection against the transmission of genital herpes, as transmission can occur to and from uncovered mucocutaneous surfaces or if the integrity of the barrier is compromised. Condoms have also been shown to be more effective in protecting women than men.
Various HSV vaccines have been under investigation for the treatment and prevention of herpes genitalis, though most have not been shown to be effective.
Women who are HSV-2 negative should be counseled to abstain from intercourse during the third trimester of pregnancy with partners that could be seropositive because primary HSV infection during this time places the fetus at highest risk of infection.
The most common approach in attempting to prevent vertical transmission is to have women with clinically apparent HSV lesions during labor undergo cesarean delivery. However, cesarean delivery does not prevent all cases of neonatal infection because in utero infection occurs and antepartum HSV cultures are not a good predictor of neonatal infections.
Use of acyclovir 400 mg PO tid during the third trimester of pregnancy has been proven to be safe and effective in preventing neonatal herpes and in eliminating the need for cesarean deliveries.
**Prognosis.**For most people, HSV infections are temporary and resolve without detrimental sequelae; however, recurrence is common.Long-term sequelae (usually CNS) are more common with neonatal HSV infection than with other types of HSV infection.

## 13.2. Herpes Zoster

**Synonyms and related keywords:** shingles, zoster

**Background.**Zoster is a common, predominantly dermal, and neurologic disorder caused by the varicella-zoster virus (VZV), a virus morphologically and antigenically identical to the virus causing varicella (chickenpox). Difference in clinical manifestations between varicella and zoster apparently depends on the

immune status of individual patients; those with no prior immunologic exposure to varicella virus, most commonly children, develop the clinical syndrome of varicella, while those with circulating varicella antibodies develop a localized recrudescence, zoster.

Zoster probably results most often from a failure of the immune system to contain latent VZV replication. Whether other factors such as radiation, physical trauma, certain medications, other infections, or stress also can trigger zoster has not been determined with certainty. Nor is it entirely clear why circulating varicella antibodies and cell-mediated immune mechanisms do not prevent recurrent overt disease, as is common with most other viral illnesses.

An inverse correlation appears to exist between the capacity of a host to mount a cellular immune response and the incidence of zoster. However, many patients with zoster apparently have normal immune systems. In these patients, zoster is postulated to occur when VZV antibody titers and cellular immunity drop to levels at which they no longer are completely effective in preventing viral invasion. Evidence for this hypothesis includes the observation that pediatricians, who presumably are reexposed to the varicella virus routinely and thus maintain high levels of immunity to VZV, seldom develop zoster.

**Pathophysiology.**Zoster most commonly manifests in 1 or more posterior spinal ganglia or cranial sensory ganglia, presumably because viral particles have been preserved within these ganglia in a dormant state since the original episode of varicella. This results in pain and characteristic cutaneous findings along the corresponding sensory dermatomes of the involved ganglia. Less often, involvement of anterior and posterior horn cells, leptomeninges, and peripheral nerves is observed, with consequent muscle weakness or palsy, pleocytosis of spinal fluid, and/or sensory loss. Rarely, myelitis, meningitis, encephalitis, or visceral involvement may occur.

**Causes.**Reactivation of varicella virus that has remained dormant within dorsal root ganglia, often for decades after the patient's initial exposure to the virus in the form of varicella (chickenpox), causes zoster. Exactly what triggers this reactivation has not yet been determined precisely, but likely candidates include external reexposure to the virus, acute or chronic disease processes (particularly malignancies and infections), medications of various types, and emotional stress. More than 1 or all of these factors, plus others, possibly are capable of triggering zoster. The reason 1 dorsal root ganglion experiences reactivation of its stored viral load preferentially over other ganglia is unclear.

The cause of PHN also remains a mystery. Rapid initiation of treatment has been shown to decrease the incidence of PHN significantly, which can be explained by the theory that incessant pain of active zoster sets up a positive feedback loop within the thalamus and the cortex, creating a central pain syndrome similar to phantom leg pain. Prompt treatment breaks the loop by providing pain-free periods early in the disease course.

**Frequency.**Internationally, the incidence of zoster has not been well studied, but probably it is in the same range of 2-3 cases per 1000 per year.

**Mortality/Morbidity.**Zoster is rarely, if ever, fatal, although in individuals who are severely debilitated, zoster may be considered a contributing factor to death. Morbidity usually is confined to pain within the affected dermatome, which can be severe and can persist well beyond the duration of active disease (postherpetic neuralgia [PHN]). Eye involvement (zoster ophthalmicus) can cause temporarily or permanently decreased visual acuity or blindness. Complications such as secondary infection and meningeal or visceral involvement can produce further morbidity in the form of infections and scarring.

**Age.**Almost 50% of individuals who live beyond age 80 years can expect to develop zoster. Zoster is rare in children and young adults, with the exception of younger patients with AIDS, lymphoma, other malignancies, and other immune deficiencies, and patients who are recipients of bone marrow and kidney transplants. In addition, patients with these associated factors are at greater risk of developing zoster regardless of age.

**History.**Zoster may begin with a systemic response, e.g. fever, anorexia, and lassitude, although symptoms frequently are mild and may not be associated by either patient or physician with the classic zoster signs and symptoms that follow. Symptoms typically include prodromal sensory phenomena along 1 or more skin dermatomes lasting 1-10 days (averaging 48 h), which usually are noted as pain or, rarely, paresthesias. Prodromal pain typically is described as muscle or toothachelike in origin but may simulate headache, iritis, pleurisy, brachial neuritis, cardiac pain, appendicitis or other intraabdominal disease, or sciatica, and it can result in incorrect tentative diagnoses. The prodromal interval of pain prior to onset of cutaneous findings has been believed to represent spread of viral particles along sensory nerves; however, approximately 10% of patients report onset of pain and rash simultaneously.

After the onset of prodromal symptoms, the following signs and symptoms occur:

Patchy erythema, occasionally accompanied by induration, appears in the dermatomal area of involvement.

Regional lymphadenopathy may appear at this stage or subsequently.

The classic finding of grouped herpetiform vesicles develops upon the erythematous base. At this point, the virus usually has induced significant inflammation of the involved sensory nerve causing severe pain, which led 19th-century French physicians to refer to zoster as "the band of roses from hell."

Cutaneous findings classically appear unilaterally (for unknown reasons), stopping abruptly at the midline of the limit of sensory coverage of the involved dermatome. Vesicles initially are clear, but eventually, they cloud, rupture, crust, and involute. This evolution often is accelerated greatly by treatment.

After vesicular involution, remaining erythematous plaques slowly resolve, typically without visible sequelae; however, scarring can occur if deeper epidermal and dermal layers have been compromised by excoriation, secondary infection, or other complications.

Unfortunately, resolution of the associated pain does not always accompany resolution of erythema and vesiculation. The PHN, which usually is confined to the

area of original dermatomal involvement, can persist for weeks, months, or years and often is severe. The reason some patients with zoster, and not others, experience PHN is not understood fully, but patients who are older (>60 y), particularly patients who are debilitated or arteriosclerotic, are affected far more frequently than patients who are younger. In addition, PHN is observed more frequently after cases of herpes zoster ophthalmicus and in instances of upper body dermatomal involvement. Other less common postherpetic sequelae include hyperesthesia, or more rarely, hypesthesia or anesthesia in the area of involvement.

The virus that causes zoster is morphologically and antigenically identical to the virus causing varicella. Experimentally, varicella has followed dermal inoculation with zoster vesicle fluid in individuals without antibodies to the virus. Susceptible individuals can contract zoster after exposure to patients with active varicella or active zoster. Whether it is possible (and if so, how likely) for individuals with varicella antibodies to contract zoster after exposure to the virus is a subject for further study and may depend on the existing antibody titer level in each individual, as well as the status of that individual's overall immune response.

**Physical.**Classic physical findings of zoster include painful grouped herpetiform vesicles on an erythematous base confined to the cutaneous surface innervated by a single unilateral sensory nerve. Regional lymphadenopathy may be present. Vesicles initially are clear but eventually cloud, rupture, crust, and involute. Many clinical variations are possible as follows:

***Herpes zoster ophthalmicus*** (HZO) constitutes 10-15% of zoster cases. HZO results from viral invasion of the Gasserian ganglion.

For unknown reasons, involvement of the ophthalmic branch of the fifth cranial nerve (CN; termed CN V1) is 5 times as common as involvement of the maxillary (CN V2) or mandibular (CN V3) branches. HZO is recognized easily by vesicular and erythematous involvement of the CN V1 dermatome, ipsilateral forehead, and upper eyelid. Ipsilateral preauricular and, occasionally, submaxillary nodal involvement is a common prodromal event in HZO and often is valued equivalently with pain, vesiculation, and erythema in establishing a diagnosis.

Prodromal lymphadenopathy should not be confused with later reactive adenopathy caused by secondary infection of vesicles. Headaches, nausea, and vomiting also are common prodrome symptoms. Signs of meningeal irritation may be present; therefore, meningitis must be excluded.

The ophthalmic branch of the fifth CN (with ciliary ganglion) sends branches to the tentorium (recurrent nerve of Arnold) and to the third and sixth (and occasionally fourth) CNs, which may account for the frequency of meningeal signs and, occasionally, the CN III and CN VI nerve palsies associated with HZO. HZO requires particularly aggressive treatment and follow-up monitoring because of the possibility of involvement of the eye, which occurs in approximately one half of patients with HZO. Traditionally, involvement of the nasociliary branch, characterized by vesicles at the tip of the nose, has indicated that eye involvement is present or imminent (termed the Hutchinson rule). However, in recent years, clinicians with extensive experience in the treatment of HZO have disputed this,

claiming that eye and nasociliary branch involvement can be present with or without distal nasal vesiculation. In the author's experience, eye lesions are rare in the absence of distal nose lesions.

Eye involvement poses a risk to vision in the absence of prompt detection and treatment. The presence of orbital edema is an ophthalmologic emergency, and patients must be referred immediately for specialized ophthalmic evaluation and treatment. Iritis, iridocyclitis, glaucoma, and corneal tissue ulcerations are possible in these cases. Involvement of the area below the palpebral fissure alone, without upper eyelid or nasal involvement, is considered less likely to result in ocular complications since the superior maxillary nerve innervates the lower eyelid.

Postherpetic complications are more common in HZO than in other manifestations of zoster. In particular, PHN is observed in well over one half of patients with HZO and can be severe and long lasting. Scarring also is more common, probably as a result of severe destructive inflammation. Palsy of the third CN, and occasionally of the fourth and sixth CNs, may occur. Rarely, simultaneous involvement of other CNs has been reported. The most common of these is seventh CN involvement, which may produce facial palsy.

***Zoster of the maxillary branch of the fifth CN*** (CN V2): involvement is localized to the ipsilateral cheek, lower eyelid, side of the nose, upper eyelid, upper teeth, mucus membrane of the nose, nasopharynx, tonsils, and roof of the mouth. At times, only the oral mucus membrane is involved without skin manifestations. Early preeruptive herpetic pain can simulate a severe toothache and result in unnecessary oral surgery or dental treatment.

***Zoster of the mandibular branch of the fifth CN*** (CN V3): areas of involvement include the side of the head, external ear and external auditory canal, lower lip, and a portion of the oral mucosa. As in other fifth CN branch involvement, prodromal pain in affected areas can result in incorrect diagnoses.

***Zoster oticus*** (also termed geniculate zoster, zoster auris, Ramsay-Hunt syndrome, Hunt syndrome): this form of zoster is considered rare but more likely is recognized rarely. It often is mistaken for eczema, Ménиre disease, Bell palsy, stroke, and abscess of the ear. Classically, it begins with otalgia and herpetiform vesicles on the external ear canal with or without features of facial paralysis resulting from facial nerve (CN VII) involvement, auditory symptoms (e.g. deafness), and vestibular symptoms in variable combinations. The syndrome also may result from zoster of ninth or tenth CN origin since the external ear has complex innervation by branches of several CNs (CN V, CN VII, CN IX, CN X), as well as vertebral nerve C2 and possibly C3.

***Glossopharyngeal and vagal zoster*** (herpes pharyngis, herpes laryngis): this variation of zoster involves the jugular and petrosal ganglia, which are adjacent and often involved in some combination; however, individual involvement of both ganglia has been observed. Painful vesicular rash typically involves the palate, posterior tongue, epiglottis, tonsillar pillars, and, occasionally, the external ear. A unilateral distribution can distinguish this variation of zoster from herpes simplex and herpangina.

***Herpes occipitocollaris*** (vertebral nerves C2 and C3 involvement): involvement includes the posterior scalp, nuchal area, portions of the ear, and portions of the lower mandible and anterior neck. Vertebral nerves C2 and C3 often are involved together. Branches of vertebral nerves C2 and C3 communicate with the seventh and tenth CNs, sometimes causing CN VII and CN X symptoms as well. Nuchal and/or scalp involvement occasionally is confused with folliculitis, furunculosis, cellulitis, erysipelas, or acne keloidalis nuchae. The painful prodrome can result in confusion and misdiagnosis until the classic vesicular rash appears.
***Zoster encephalomyelitis*** (meningoencephalitis): localized mild leptomeningitis in the region of neurologic involvement is more common than generally is recognized and often results in pleocytosis (25-50 lymphocytes) in the spinal fluid.
***Zoster myelitis***: that VZV can produce encephalomyelitis is well documented. More rarely, the myelitis lesion predominates or is the sole feature. The clinical picture is one of acute onset of paraplegia resulting from a diffuse involvement of the spinal cord. The picture is that associated with acute transverse myelopathy.
***Disseminated zoster***: dissemination usually is defined as a generalized eruption of more than 10-12 extradermatomal vesicles occurring 7-14 days after the onset of classic dermatomal zoster. Disseminated zoster typically is indistinguishable clinically from varicella (chickenpox). Patients in whom zoster has disseminated must be observed carefully for the development of pneumonitis and encephalitis, which can be life threatening.
***Bilateral zoster***: on rare occasions, zoster manifests bilaterally. The reason this occurs is unknown, as is the reason zoster typically occurs unilaterally. A popular superstition among lay people states that "if shingles occurs on both sides and meets in the middle, you will die." While some cases of bilateral zoster have been reported in patients who are extremely debilitated and in whom bilateral presentation cannot be considered a favorable sign, a fatal prognosis is not necessarily indicated for all patients. In cases of bilateral zoster, it is not unusual for 1 or 2 adjacent dermatomes to be involved. Unlike examples of multiple dermatomal involvement in unilateral disease, involvement in adjacent dermatomes is not typically a sign of underlying disease (e.g. malignancy).
***Multiple dermatomal involvement***: involvement of more than 1 dermatomal distribution in unilateral zoster is rare and usually is considered a harbinger of significant compromise of the immune system caused by AIDS, malignancy, chemotherapy, and other factors.
***Recurrent zoster***: recurrences, while rare, are not unheard of and have not been shown to represent any specific event. Most reputed cases of recurrent zoster involve other entities, usually herpes simplex in a linear distribution.
***Zoster involving the urinary bladder***: rarely, zoster involving the dermatomes of the buttock area (vertebral nerves L1, L2, S2, S3, S4) may be associated with vesicles in the bladder, which can cause severe dysuria and urinary frequency. This picture can be mistaken easily for cystitis. If vesicles rupture in the bladder, hematuria (another common symptom of cystitis) may occur. Transient bladder paralysis resulting from zoster involving the gluteal and sacral regions and lumbar

sympathetic segments has been reported, and acute urinary retention is possible if a motor component exists.

***Other internal manifestations***: vesicular involvement has been reported in bronchi, pleural spaces, and the gastrointestinal tract. Zoster pneumonia also has been reported. Such involvement frequently is found in individuals with significantly compromised immune systems. Pain in these areas, as on the cutaneous surface, may be referred pain and does not necessarily indicate the presence of vesicles.

***Motor complications***: while zoster classically invades only sensory nerves (for unknown reasons), viral particles occasionally cross over to the anterior horn of the involved ganglion, resulting in motor symptoms. Paresis may be seen in extraocular muscles, any area of facial innervation, and anywhere along the spinal cord, including the phrenic nerve. Paresis most commonly is observed when muscles of an arm or leg are involved; however, this may be because it is detected most easily at those locations. Truncal motor involvement may be more common than generally is believed, because both physician and patient easily may overlook a small area of muscle weakness of the central trunk.

Motor symptoms can range from weakness to total paralysis, depending on how many roots of the involved nerve plexus are affected. While most motor involvement (like most sensory involvement) is self-limited, partial or complete paresis can persist indefinitely, particularly when CN V, CN VII, phrenic, and upper or lower extremity nerves are affected. Paralysis of abdominal musculature can cause a hernial bulge.

**Complications.**Pain within the affected dermatome can be severe and can persist well beyond the duration of active disease (PHN). Eye involvement (zoster ophthalmicus) temporarily or permanently can cause decreased visual acuity or blindness. Complications such as secondary infection and meningeal or visceral involvement can produce further morbidity in the form of infections and scarring.Zoster is rarely, if ever, fatal, although in individuals who are severely debilitated, zoster may be considered a contributing factor to death.

**Lab Studies.**Systemic manifestations are uncommon and usually are confined to patients in whom the immune system has been compromised by other disease processes or chemotherapy. General laboratory studies and other systemic workup are not indicated unless complications or underlying diseases are suggested. A small percentage of patients, particularly those with CN involvement, may develop headache and neck stiffness, necessitating a spinal tap to exclude meningitis.

Occasionally, Tzanck preparation, viral culture, direct fluorescence antibody (DFA) testing, and/or skin biopsy may be necessary to establish the diagnosis in atypical cases. DFA testing is more sensitive than conventional viral cultures because of the lability of VZV.

Zoster is seen approximately 7 times more frequently in patients infected by human immunodeficiency virus (HIV); therefore, when clinically indicated, order an HIV test.

**Histologic Findings.**Clinical diagnosis almost always can be made. Biopsy is reserved for cases difficult to diagnose. On rare occasions when biopsy is necessary, histologic findings are similar to those of herpes simplex and varicella (chickenpox). Ballooning degeneration and acantholysis of keratinocytes result in an intraepidermal vesicle. Multinucleated giant cells with accentuation of nuclear material at the periphery of nuclei are characteristic. Underlying leukocytoclastic vasculitis often is a prominent finding and helps differentiate zoster from other herpetic infections.

**Medical Care.**Until recently, treatment of zoster has been frustrating because of a fundamental lack of effective antiviral medications; however, this did not prevent many clinicians from making the attempt. An enormous number and variety of therapeutic approaches to the treatment of zoster have been proposed over the years, most of which probably are ineffective. Reports of anecdotal evidence of efficacy are difficult to evaluate objectively because of the highly variable and self-limited nature of the disease.

***Systemic steroids***. Many practitioners have long used oral prednisone and similar medications to reduce pain and to decrease the incidence of PHN, presumably by reducing inflammation in dorsal root ganglia and involved sensory nerves. While never conclusively demonstrated in a double-blind crossover study, some evidence exists that steroids are effective in achieving these treatment goals. More study is needed.

A substantial dose (40-60 mg every morning) typically is administered as early as possible in the course of the disease and is continued for 1 week, followed by a rapid taper over 1-2 weeks.

Dissemination of viral particles beyond dermatomal limits always has been a theoretical concern, but clinically, it almost never is observed in individuals with intact immune systems. Typical risks inherent in the use of systemic steroids, such as adrenocortical suppression and femoral osteonecrosis, must be kept in mind.

***Systemic antiviral agents.*** Controversy over use of systemic steroids has been rendered all but moot in recent years with the advent of effective antiviral agents. Acyclovir and its derivatives (valacyclovir, famciclovir, penciclovir, and desciclovir, which is not available in the US) all have been shown to be safe and effective in the treatment of active disease and in the prevention of PHN.

Usually, the earlier antiviral medications are started, the more effective they are in shortening the duration of zoster and in preventing or decreasing severity of PHN. Ideally, initiate therapy within 72 hours of the onset of symptoms.

***Varicella-zoster vaccine.*** Since 1995, live attenuated varicella virus vaccine (Varivax) has been available in the US and has been up to 99% effective in protecting susceptible individuals from varicella infection. It also may prove effective in prevention of zoster.

***Varicella-zoster immune globulin***. The Centers for Disease Control and Prevention (CDC) currently recommend administration of varicella-zoster immune globulin (VZIG) to prevent or modify clinical illness in persons with exposure to varicella or zoster who are susceptible or immunocompromised. VZIG provides

maximum benefit when administered as soon as possible after the presumed exposure, but VZIG may be effective if administered as late as 96 hours after exposure. Protection after VZIG administration lasts for an average of approximately 3 weeks, according to the CDC.

***Management of PHN.*** Pain associated with zoster usually is the most debilitating symptom of the disease. Once established, pain is notoriously difficult to alleviate with traditional analgesics, including narcotics.

Initiation of antiviral therapy as early as possible in the course of acute zoster, and definitely within 72 hours of onset, has been shown to be effective in alleviating acute pain and preventing PHN in most patients. Once PHN has developed, treatment is much more difficult and often impossible.

Topical capsaicin commonly is recommended; its active ingredient depletes neurotransmitters at involved nerve endings. However, the cream must be applied at least 5 times per day to be effective, and pain may increase upon application for the first few days of therapy as accumulated neurotransmitters are released. Once neurotransmitter reserves have been depleted, any resultant pain relief is temporary. Tricyclic antidepressants and the anticonvulsant drug gabapentin have been used with variable success.

**Consultations.**Consultation with the appropriate specialist may be indicated when symptoms point toward meningitis (herpes zoster ophthalmicus), dental disease (zoster of maxillary branch), ear infections or deafness (Ramsay-Hunt syndrome), oropharyngeal infections (zoster pharyngis/laryngis), meningoencephalitis, and encephalomyelitis; when motor complications are present; or when the urinary bladder, lungs, or gastrointestinal tract are involved.

**Prevention.** Since 1995, live attenuated varicella-virus vaccine (Varivax) has been available in the US and has been up to 99% effective in protecting susceptible individuals from varicella infection. It also may prove effective in prevention of zoster.

**Prognosis** is excellent, although the pain of PHN, when it occurs, can range in intensity from uncomfortable to debilitating.

## 13.3. Molluscum Contagiosum

**Backgroun.**Descriptions of molluscum contagiosum have been in the medical literature since 1817. In 1905, the viral nature of molluscum contagiosum was discovered by Juliusburg. It is a cutaneous infection caused by a large DNA poxvirus that affects both children and adults. Transmission has been reported by direct skin contact and has occurred in wrestlers, patients of a surgeon with a hand lesion, and children sharing baths, towels, gymnasium equipment, and benches. Autoinoculation also occurs as evidenced by linear arrays of lesions on infected individuals.

**Pathophysiology.**The virus replicates in the cytoplasm of epithelial cells producing cytoplasmic inclusions, and it may cause enlargement of infected cells.

**Causes.**DNA poxvirus, the largest virus known (200 X 300 X 100 nm), causes molluscum contagiosum. The inner and outer membranes of the virion surround a dumbbell-shaped nucleoid. The genome is a linear duplex DNA with an estimated weight of 120-200 megadaltons. Restriction endonuclease analysis of the molluscum contagiosum virus (MCV) reveals 2 viral subtypes named MCV 1 and MCV 2 with genomes of 185 kilobases (kb) and 195 kb, respectively.MCV encodes an antioxidant protein (MC066L), selenoprotein, which functions as a scavenger of reactive oxygen metabolites and protects cells from UV or peroxide damage. The particular role of this protein is not known because the attempt to grow MCV in vitro has not been successful.

**Frequency.** Molluscum contagiosum is common in the tropics and subtropics probably because of the increased desquamation associated with hydration. Epidemiological studies suggest that transmission may be related to poor hygiene and climatic factors, such as warmth and humidity.

**History.** Most patients are asymptomatic; some complain of pruritus, tenderness, and pain.The incubation period ranges from weeks to months (14-50 d). If patients have eczema or other diseases altering skin barrier function, molluscum may spread more rapidly in affected areas.

**Physical.**Physical findings generally are limited to the skin, but cases have reported findings on the eyelids and conjunctiva.

***Skin - Primary lesion.*** Firm, smooth, umbilicated papules, usually 2-6 mm in diameter (range 1-15 mm) may be present in groups or widely disseminated on the skin and mucosal surfaces. Lesions greater than 15 mm have been described, particularly in patients with AIDS.The lesions can be flesh-colored, white, translucent, or even yellow in color.The number of lesions varies from 1-20 up to hundreds in some reports.Some lesions become confluent to form a plaque.Lesions generally are self-limited but can persist for several years.

***Skin – Distribution.*** In children, lesions mainly on the trunk and extremities.In adults, lesions often are located on the lower abdominal wall, inner thighs, pubic area, and genitalia.Although rarely found in the mouth or on the palms and soles, cases of molluscum contagiosum involving the oral mucosa, including the lips, buccal mucosa, hard palate, retromolar pad, and tongue, have been reported.

***Immunocompromised conditions***. In some conditions, including sarcoidosis, lymphocytic leukemia, congenital immunodeficiency, selective immunoglobulin M (IgM) deficiency, thymoma, treatment with prednisone and methotrexate, AIDS, malignancy, and atopic dermatitis, multiple widespread, persistent, disfiguring lesions can occur, especially on the face and possibly involving the neck and trunk.

**Complications** include irritation, inflammation, and secondary infections. Lesions on eyelids may be associated with follicular or papillary conjunctivitis.

**Lab Studies.** Generally, diagnosis is made on clinical grounds based on appearance of the lesions.Identification of characteristic intracytoplasmic inclusion bodies in histologic or cytologic preparations is made by hematoxylin and eosin (H&E) staining of biopsy sections.

Lab: Serum antibodies have been measured by complement fixation, tissue culture neutralization, fluorescent antibody, and gel agar diffusion techniques; however, they are not well standardized.Smears from scrapings of lesions stained by Papanicolaou or Wright, Giemsa, or Gram reveal inclusion bodies.Antigen of MCV may be identified by fluorescent antibody technique.

**Other Tests.** Electron micrographs of fixed material from papule are taken. Sexually active patients also may have other concomitant venereal diseases such as syphilis and gonorrhea, so their partners also should be examined to prevent reinoculation.

**Histologic Findings.** The epidermis is acanthotic and may measure up to 6 times the normal thickness. Basal cells are slightly larger and more columnar than normal, with dense and granular nuclei. Above the basal keratinocytes are enlarged keratinocytes with a deep purple appearance. The molluscum body is the result of a virally induced cytoplasmic transformation that begins in the lower cells of the epidermis, just above the basal cell layer. Keratinocytes contain multiple Feulgen-positive intracytoplasmic inclusion bodies (Henderson-Patterson or molluscum bodies) containing viral particles that can be identified in the cells of stratum spinosum. The viral particles increase in size as they progress up toward the granular layer causing compression of the nucleus to the periphery of the infected keratinocytes. The core of the down-growth of the central stratum corneum of the papules is largely replaced by viral particles. The dermis under the infected lobule of epidermis is normal except for occasional inflammation.

**Medical Care.**Molluscum contagiosum generally is self-limited and heals after several months or years. Any one lesion is present for about 2 months; however, to prevent autoinoculation or transmission to close contacts, therapy may be beneficial. The common goal of the different treatment methods is the destruction of the lesions. Controlled studies have not been completed with the various treatments. Commonly used treatments are not approved by the Food and Drug Administration (FDA).

***Topical applications.*** Cantharidin - a single application that may need to be repeated once or twice every 3-4 weeks.Tretinoin - cream 0.1% or gel 0.025% applied daily. Podophyllin. Trichloroacetic acid. Tincture of iodine. Silver nitrate or phenol. Cryotherapy with liquid nitrogen.

***Systemic agents***: Griseofulvin, Methisazone, Cimetidine. In immunocompromised patients, improvement of lesions was seen in individual cases with the use of ritonavir, cidofovir (intravenous and topical), AZT, intralesional interferon alpha, and topical injections of streptococcal antigen OK-432.

**Surgical Care.**Curettage followed either by light electrodesiccation or by application of a caustic agent to cauterize bleeding points has been shown to be an effective treatment in children and adults. The topical anesthetic cream EMLA (eutectic mixture of local anesthetics) can be applied under occlusion an hour before curettage to decrease the discomfort associated with the procedure.

**Prognosis.**Molluscum contagiosum is a benign self-limited disease.Treatments are effective.Overall, prognosis is excellent.

## 13.4. Genital Warts

**Synonyms and related keywords:** condyloma acuminatum, GW

**Background.**Until the 19th century, genital warts (GW) were believed to be a form of syphilis or gonorrhea. The viral etiology of warts was established in 1907 by inoculation of wart filtrates into skin, inducing papillomas at the injection site. Today, condyloma acuminatum or GW generally are recognized as benign proliferations of the anogenital skin and mucosa that result from infection with human papilloma viruses (HPV). The HPV family has at least 78 well-documented genotypes. Some believe that the number of HPV types eventually will reach 100 or more. Despite the generally benign nature of the proliferations, certain types of HPV can place patients at a high risk for anogenital cancer.

**Pathophysiology.**GW are a result of HPV infection, which is believed to be acquired by inoculation of the virus into the epidermis via defects in the epithelium (e.g. maceration of the skin). Autoinoculation of virus into opposed lesions is common. Spread of HPV infection is usually through skin-associated virus and not from blood-borne infection. Probably, cell-mediated immunity (CMI) plays a significant role in wart regression; patients with CMI deficiency are particularly susceptible to HPV infection and are notoriously difficult to treat.

**Frequency.** GW have affected as many as 30 million individuals worldwide.

**Mortality/Morbidity.** Although anogenital warts generally are benign, their significance is drawn from the increased risk of malignancy secondary to HPV infection. Specifically, HPV types 16, 18, 31, 33, and 51 are associated with the greatest prevalence of anogenital malignancy. Infectivity of anogenital warts may be up to two thirds of sexual contacts. High concordance for the same HPV type has been found among sexual partners.

**Age.** The highest incidence of GW consistently is found in young adults aged 15-25 years. This observation tends to hold true even after adjustment for lifetime number of sexual partners, which itself is a significant risk factor for HPV infection.

**Causes.**The definitive cause of anogenital warts is HPV. HPV is part of the papovavirus class, which includes SV 40, BK, and JC virus. The HPV capsid lacks an envelope, which makes it very stable and resistant to various treatments.No serologic typing of HPV is available because of the lack of consistent in vitro culture methods.Typing of HPV is according to genotype, which usually is determined by molecular hybridization techniques using molecularly cloned HPV DNA of known type as the standard.Two HPV are said to be of different types when their DNA hybridize (bind) less than 50% as efficiently to each other as to themselves.More than 30 types of HPV (of nearly 80 sequenced to date) have been found in genital warts. They are very host specific. These viruses do not infect laboratory animals and are not susceptible to acyclovir.As a rule, HPV types

causing common warts of the skin do not infect moist epithelium and vice versa.Multiple clinical associations with unique genotypes of HPV have been documented. HPV types and their association with the clinical disease are as follows: plantar warts - 1, 2, 4, and 63; common warts - 2, 4, 1, 26, 27, 29, 57, 65, and 75-78; meat/poultry/fish handlers - 7, 1-4, 10, and 28; flat warts - 3, 10, 27, 28, 38, and 49; epidermodysplasia verruciformis - 2, 3, 5, 8, 9, 10, 12, 14, 15, 17, 19, 20, 21-25, 28, 36-38, 40, 47, and 50;squamous cell carcinoma or actinic keratosis - 16, 14, 18, 36, and 41; squamous cell carcinoma, keratoacanthoma type - 37, 7, 9, 16, 29, 35, and 58;squamous cell carcinoma, in immunocompromised - 48 and 60; Bowen disease (non-genital) - 16, 2, 3, 5, 16, 18, 20, 26-29, 31, 33, 34, 54, 56, 58, 61, 62, and 73;melanoma – 38; oral focal epithelial hyperplasia - 13 and 32; oral papilloma - 11, 7, 32, 57, 72, and 73; laryngeal papilloma (recurrent respiratory papillomatosis) - 6, 11, 2, 16, 30, 40, and 57;conjunctival papillomas and cancer - 6, 11, and 16; epidermal cyst – 60; condyloma acuminatum - 6, 11, 1-5, 10, 16, 18, 30, 31, 33, 35, 39-45, 51-59, and 70; giant condyloma of Buschke and Löwenstein and other verrucous carcinoma - 6, 11, 57, 72, and 73; Bowenoid papulosis - 16, 34, 39, 40, 42, and 45; vulvar intraepithelial neoplasia - 56, 59-64, 67, and 71; cervical squamous intraepithelial lesions (SIL); low-grade squamous intraepithelial lesions (LGSIL) - 6, 11, 16, 18, 26, 27, 30, 31, 33-35, 40, 42-45, 51-58, 61, 62, 67-69, and 71-74; High-grade squamous intraepithelial lesions (HGSIL) - 16, 18, 6, 11, 31, 33, 35, 39, 42, 44, 45, 51, 52, 56, 58, 59, 61, 64, 66, and 68; cervical cancer - 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68.

**History.**Warts generally do not become clinically apparent until several months after inoculation with HPV.Lesions follow a slow and indolent course and may develop by inoculation from opposing surfaces.

**Physical.**Anogenital warts consist of pink-to-brown papillomatous papules or nodules of the genitalia, perineum, crural folds, and anus.Warts vary in size and can form large, exophytic, cauliflowerlike masses. Discrete papules, 1-3 mm in size can present on the shaft of the penis. The growth can extend into the vagina, urethra, cervix, perirectal epithelium, anus, and rectum.

**Complications.** Disease complications can include progression to malignancy and transmission to other sexual contacts. In the setting of GW active during a pregnancy delivery, there is a small risk of laryngeal papillomatosis.Each therapeutic modality carries its own unique set of risks. Risks of individual medical options are enumerated above.Expected effects of cryosurgery include pain, edema, vesicles, bullae, weeping, and some necrosis. There is a small risk of infection, bleeding, abnormal scarring, pigment alteration, paresthesias, and alopecia with cryosurgery.Similarly, laser surgery of GW may result in pigment alteration, abnormal scarring, and infection. Special care must be taken to prevent respiratory infection from the laser plume generated by vaporization of virally infected tissue.

**Lab Studies.** Diagnosis usually is made clinically; it may be helped by the application of acetic acid and biopsy.At the current time, identification of precise HPV genotypes is available only in research laboratories by using DNA

hybridization techniques. This technique includes Southern blot (highly sensitive and also most time consuming), dot blot, and in situ hybridization.Others methods include enzyme-linked immunosorbent assay (ELISA) for immunoglobulin G (IgG) antibody (Ab) against HPV 16 capsid.Certain screening tests are available with a relatively high sensitivity and specificity; they include the following: ViraPap, ThinPrep Pap, Hybrid capture II.

**Other Tests.** Acetic acid test. Soaking acetic acid into suspicious lesions can enhance the degree of suspicion in lesions without classic features.The method involves applying a 3-5% acetic acid–moistened gauze pad for 5-10 minutes on suspected lesions of the penis, cervix, labia, or perianal area.Inconspicuous, flat, genital lesions that might be difficult to assess become visible. Dysplastic and neoplastic tissues turn white (acetowhite).False-positive results are common and can result from anything that causes parakeratosis (e.g. candidiasis, psoriasis, lichen planus, healing epithelium, sebaceous glands).This technique can be combined with the use of colposcopy to examine cervical lesions.

**Histologic Findings.** Histopathology can elucidate diagnosis in most cases. Verrucae consist of acanthotic epidermis with papillomatosis, hyperkeratosis, and parakeratosis. Elongated rete ridges may point to the center of the wart and dermal capillary vessels may be thrombosed. Koilocytes are indicative of HPV infection. These are large keratinocytes with an eccentric, pyknotic nucleus surrounded by a perinuclear halo. Anogenital warts lack a granular layer and tend to be more papillomatous and vascular than common warts. An electron microscope may show viral particles in nuclei. Immunohistochemical staining with the peroxidase-antiperoxidase technique stains cells infected by viral particles.

**Medical Care.** Treatment is aimed at destruction of the warty growths rather than elimination of the virus. Subclinical infection probably is lifelong, and there is no cure. Most partners are likely to be subclinically infected with HPV, even if they do not have exophytic lesions. Use of condoms may reduce transmission of the virus to uninfected partners.Standard therapies for GW can remove most warts; however, there is no ideal treatment for all warts and all patients.Caustics/acids - 80-90% bichloroacetic acid (BCA) or trichloroacetic acid (TCA). Podophyllin resin - 10-25% or 0.5% podofilox solution or gel (Condylox). Imiquimod 5% cream (Aldara) - 3 times per week, up to 4 months. Interferon, intramuscular or intralesional injection - 3 million units, 3 times per week for 3 weeks.

HPV vaccines (not yet available). A variety of prophylactic and therapeutic HPV vaccine trials are ongoing and may be of potential future benefit. Notably, a vaccine for HPV 16 is currently in a phase II control trial, a TA-GW vaccine is underway in a phase II open trial, and a clinical trial for a multivalent vaccine for HPV 16/18/31/45/6 is about to start.

**Surgical Care.** Cryosurgery is very effective for treating multiple, small, genital warts.Warts on the shaft of the penis and vulva respond very well to cryotherapy.Cryotherapy of the rectum is painful and less successful.Cryotherapy is effective and safe for the mother and fetus when used during the second and third trimesters of pregnancy.Electrosurgery is quite effective for a limited number

of lesions on the shaft of the penis.Large, unresponsive lesions around the rectum or vulva can be treated with scissor excision of the bulk of the mass followed by electrocautery of the remaining tissue down to the skin surface.
Loop electrocautery excisional procedure (LEEP) after colposcopical biopsy has become a standard procedure for cervical lesions particularly for the ones with neoplastic features. Removal of a very large mass of warts is a painful procedure, best performed under either general or spinal anesthesia.
Carbon dioxide laser is an efficient method of treating primary and recurrent anogenital warts because of its precision and rapid healing without scarring.Primary cure rates as high as 91% have been reported. Carbon dioxide laser is the treatment of choice for pregnant women with extensive lesions or lesions that do not respond to TCA. Pulsed-dye laser and other new lasers have been used by some with various successful rates.Surgery is indicated particularly for large GW or malignant lesions. For recurrent carcinoma, Mohs surgery is a good choice.
**Prognosis** is good, and most cases of GW are amenable to treatment. Patients who are immunosuppressed with GW may represent a special challenge.

## 13.5. Non-genital Warts

**Background.** Warts are benign proliferations of skin and mucosa caused by human papilloma viruses (HPV). Currently, more than 150 types of HPV have been identified. Certain HPV types tend to occur at particular anatomic sites; however, warts of any HPV type may occur at any site. The primary clinical manifestations of HPV include common warts, genital warts, flat warts, and deep palmoplantar warts (myrmecia). Less common manifestations of HPV include focal epithelial hyperplasia (Heck disease), epidermodysplasia verruciformis, and plantar cysts. Warts are transmitted by direct or indirect contact, and predisposing factors include disruption to the normal epithelial barrier. Treatment can be difficult, with frequent failures and recurrences; however, many warts resolve spontaneously within a few years.
A small subset of HPV types is associated with the development of malignancies, including types 6, 11, 16, 18, 31, and 35. Malignant transformation most commonly is seen in patients with genital warts and in immunocompromised patients. HPV types 5, 8, 20, and 47 have oncogenic potential in patients with epidermodysplasia verruciformis.
**Pathophysiology.** Warts can affect any area on the skin and mucous membranes. Infection is confined to the epithelium and does not result in systemic dissemination of the virus. Replication occurs in differentiated epithelial cells in the upper level of the epidermis; however, viral particles can be found in the basal layer.
**Causes.** Warts are caused by HPV, which is a double-stranded, circular, supercoiled DNA virus enclosed in an icosahedral capsid and comprising 72

capsomers. More than 150 types of HPV have been identified. Common warts - HPV types 2 and 4 (most common), followed by types 1, 3, 27, 29, and 57. Deep palmoplantar warts (myrmecia) - HPV type 1 (most common), followed by types 2, 3, 4, 27, 29, and 57. Flat warts - HPV types 3, 10, and 28. Butcher's warts - HPV type 7. Focal epithelial hyperplasia (Heck disease) - HPV types 13 and 32. Cystic warts - HPV type 60.

**Frequency.** Warts are widespread in the worldwide population. Although the frequency is unknown, warts are estimated to affect approximately 7-12% of the population. In school-aged children, the prevalence is 10-20%. An increased frequency also is seen among immunosuppressed patients and meat handlers.

**Mortality/Morbidity.** Common warts usually are asymptomatic, but may cause cosmetic disfigurement or tenderness. Plantar warts usually are painful, and extensive involvement on the sole of the foot may impair ambulation. Malignant change in non-genital warts is rare but has been reported and is termed verrucous carcinoma. Verrucous carcinoma is considered to be a slow growing, locally invasive, well-differentiated squamous cell carcinoma that easily may be mistaken for a common wart. It can occur anywhere on the skin but is most common on the plantar surface.

**Age.** Warts can occur at any age. They are unusual in infancy and early childhood, increase in incidence among school-aged children, and peak at 12-16 years.

**History.** HPV is spread by direct or indirect contact. It can resist desiccation, freezing, and prolonged storage outside of host cells. Autoinoculation also may occur, causing local spread of lesions. The incubation period for HPV ranges from 1-6 months; however, latency periods of up to 3 years or more are suspected.

**Physical**

***Common warts***: common warts also are termed verruca vulgaris. They appear as hard papules with a rough irregular scaly surface. They range from smaller than 1 mm to larger than 1 cm. They can occur on any part of the body but are seen most commonly on the hands and knees.

***Filiform warts***: filiform warts are long slender growths, usually seen on the face around the lips, eyelids, or nares.

***Deep palmoplantar warts*** (myrmecia): deep palmoplantar warts also are termed myrmecia. They begin as small shiny papules and progress to deep endophytic, sharply defined, round lesions with a rough keratotic surface, surrounded by a smooth collar of thickened horn. Because they grow deep, they tend to be more painful than common warts. Myrmecia warts that occur on the plantar surface usually are found on weight-bearing areas, such as the metatarsal head and heel. When they occur on the hand, they tend to be subungual or periungual.

***Flat warts***: flat warts also are termed plane warts or verruca plana. They are characterized as flat or slightly elevated flesh-colored papules that may be smooth or slightly hyperkeratotic. They range from 1-5 mm or more, and numbers range from a few to hundreds of lesions that may become grouped or confluent. These warts may occur anywhere; however, the face, hands, and shins tend to be the most common areas. They may appear in a linear distribution as a result of scratching or

trauma (Koebner phenomenon). Regression of these lesions may occur, which usually is heralded by inflammation.

***Butcher's warts***: Butcher's warts are seen in people who frequently handle raw meat. Their morphology is similar to common warts, with a higher prevalence of hyperproliferative cauliflowerlike lesions. They are seen most commonly on the hands.

***Mosaic warts***: a mosaic wart is a plaque of closely grouped warts. When the surface is pared, the angular outlines of tightly compressed individual warts can be seen. These usually are seen on the palms and soles.

***Focal epithelial hyperplasia*** (Heck disease): focal epithelial hyperplasia, also termed Heck disease, is an HPV infection occurring in the oral cavity, usually on the lower labial mucosa. It also can be seen on the buccal or gingival mucosa and rarely, on the tongue. The lesions appear as multiple flat-topped or dome-shaped pink-white papules. They usually are 1-5 mm, with some lesions coalescing into plaques. They are seen most frequently in children of American Indian or Eskimo descent.

***Cystic warts*** (plantar epidermoid cysts): a cystic wart appears as a nodule on the weight-bearing surface of the sole. The nodule usually is smooth with visible rete ridges but may become hyperkeratotic. If the lesion is incised, cheesy material may be expressed. The etiology of these lesions is uncertain. One theory is that a cyst forms, originating from the eccrine duct, and secondary HPV infection occurs. Another theory is that the epidermis infected with HPV becomes implanted into the dermis, forming an epidermal inclusion cyst.

**Lab Studies.**The diagnosis of warts is made primarily on the basis of clinical findings. Immunohistochemical detection of HPV structural proteins may confirm the presence of virus in a lesion, but this has a low sensitivity.Viral DNA identification using Southern blot hybridization is a more sensitive and specific technique used to identify the specific HPV type present in tissue.Polymerase chain reaction may be used to amplify viral DNA for testing. Although HPV may be detected in younger lesions, it may not be present in older lesions.

**Procedures.**Paring of warts may reveal minute black dots, which represent thrombosed capillaries.Obtain a biopsy if doubt exists regarding the diagnosis.

**Histologic Findings.*Common warts***: histopathologic features of common warts include digitated epidermal hyperplasia, acanthosis, papillomatosis, compact orthokeratosis, hypergranulosis, dilated tortuous capillaries within the dermal papillae, and vertical tiers of parakeratotic cells with entrapped red blood cells above the tips of the digitations. Elongated rete ridges may point radially toward the center of the lesion. In the granular layer, HPV-infected cells may have coarse keratohyaline granules and vacuoles surrounding wrinkled-appearing nuclei. Koilocytic (vacuolated) cells are pathognomonic for warts.

***Deep palmoplantar warts*** (myrmecia): deep palmoplantar warts appear similar to common warts except that most of the lesion lies deep to the plane of the skin surface. This endophytic epidermal growth often has the distinctive feature of polygonal, refractile-appearing, eosinophilic, cytoplasmic inclusions composed of

keratin filaments, forming ringlike structures. Basophilic nuclear inclusions and basophilic parakeratotic cells loaded with virions may be in the upper layers of the epidermis.

***Flat warts***: flat warts resemble common warts on light microscopy; however, the features tend to be muted. Cells with prominent perinuclear vacuolization around pyknotic, strongly basophilic, centrally located nuclei may be in the granular layer. These may be referred to as "owl's eye cells."

***Butcher's warts:*** Butcher's warts have prominent acanthosis, hyperkeratosis, and papillomatosis. Small vacuolized cells with centrally located shrunken nuclei may be seen in clusters within the granular layer rete ridges.

***Filiform warts***: filiform warts may appear similar to common warts but tend to have prominent papillomatosis.

***Focal epithelial hyperplasia*** (Heck disease): focal epithelial hyperplasia is characterized by a hyperplastic mucosa with thin parakeratotic stratum corneum, acanthosis, blunting and anastomosis of rete ridges, and pallor of epidermal cells as a result of intracellular edema. Some areas may have prominent keratohyaline granules, and some vacuolated cells may be present.

***Cystic warts***: a cyst filled with horny material characterizes cystic warts. The wall is composed of basal, squamous, and granular cells. Many of the epithelial cells may have large nuclei and clear cytoplasm with eosinophilic inclusion bodies. The cyst may rupture, resulting in a foreign body granuloma.

**Medical Care.**Multiple modalities are available for the treatment of warts, but none is uniformly effective. Start with the least painful, least expensive, and least time-consuming methods. Reserve the more expensive and invasive procedures for refractory extensive warts. Treatment methods are as follows:

***Benign neglect***. Providing no treatment at all is certainly safe and cost effective. Consider this as an option, since 65% of warts may regress spontaneously within 2 years. Without treatment, however, patients risk warts that may enlarge or spread to other areas. Non-treatment is not recommended for patients with extensive, spreading, or symptomatic warts or in warts that have been present for more than 2 years.

***Topical agents.*** Salicylic acid is a first-line therapy used to treat warts. Many preparations are available over the counter. Therapeutic effects are enhanced by removing surface keratin or by occlusion with adhesive plasters. Cure rates from 70-80% are reported. Salicylic acid is available without a prescription and can be applied by the patient at home.

Several topical agents are available for treating warts that can be applied by trained personnel in a physician's office. These include cantharidin, dinitrochlorobenzene, dibutyl squaric acid, trichloroacetic acid, and podophyllin.

Cantharidin is dried extract of the blister beetle, also termed Spanish fly. It causes epidermal necrosis and blistering. Use cantharidin with caution because of its potential to cause blistering of normal surrounding skin. This treatment may require weekly repetition.

Dinitrochlorobenzene (DNCB) is a powerful sensitizing agent that induces an allergic contact dermatitis that causes local inflammation and an immune response. Dibutyl squaric acid is a contact sensitizer. Unlike DNCB, it is not a mutagen, and therefore, may be a safer alternative.

Trichloroacetic acid is a caustic compound that causes immediate superficial tissue necrosis. Use it in concentrations up to 80%. It may require weekly applications.

Podophyllin is a resin extract derived from the May Apple plant that contains several cytotoxic compounds. Use with caution, since it has a powerful irritant effect. Podophyllin works better on mucosal surfaces, and therefore, is used more commonly for treating genital warts. Reportedly, podophyllin has been successful in treating persistent plantar warts.

Several prescription medications have proven beneficial in treating warts. These include imiquimod, cidofovir, podophyllotoxin, 5-fluorouracil, and tretinoin.

Imiquimod is a potent stimulator of proinflammatory cytokine release. Currently, it has been approved only for treating genital warts; however, it shows promise in treating common warts as well. Cidofovir is an antiviral agent that is a nucleotide analog of deoxycytidine monophosphate. It has been used for refractory condyloma acuminata and recurrent genital herpes. Podophyllotoxin is a purified ingredient of podophyllin. Since it tends to work better on mucosal surfaces, it also is used primarily to treat genital warts. 5-Fluorouracil is a topical chemotherapeutic agent primarily used to treat actinic keratoses. It is effective in treating warts when used under occlusion daily for up to 1 month. Tretinoin is a topical retinoic acid that primarily is used to treat acne. It has been successful in treating flat warts.

***Intralesional Injections***: when warts are persistent and refractory to topical agents, consider intralesional injections of either bleomycin or interferon alpha as an alternative. Bleomycin is a cytotoxic polypeptide that inhibits DNA synthesis in cells and viruses. The limiting side effects of bleomycin include pain with injection, local urticaria, Raynaud phenomenon, and possible tissue necrosis. Used periungually, bleomycin may cause nail dystrophy or loss. Reserve bleomycin as a third-line treatment when standard therapies have failed.

Interferon alpha is a naturally occurring cytokine with antiviral, antibacterial, anticancer, and immunomodulatory effects. Intralesional administration is more effective than systemic administration and is associated only with mild flulike symptoms. Treatments may be required for several weeks to months before beneficial results are seen. Consider this treatment as third line, and reserve it for warts that are resistant to standard treatments.

***Systemic agents***: two systemic agents used to treat warts include cimetidine and retinoids. Cimetidine is a type-2 histamine receptor antagonist commonly used to treat peptic ulcer disease. Because of its immunomodulatory effects, cimetidine was considered a possible treatment for warts; however, results have varied.

Retinoids are synthetic vitamin A analogs that may help with extensive disabling hyperkeratotic warts in immunocompromised patients. They may help alleviate pain and facilitate the use of other treatments. Retinoids also have helped reduce the number of lesions in immunosuppressed renal transplant patients. The limiting

side effects include liver function abnormalities, increased serum lipid levels, and teratogenicity.

***Alternative treatments***: several alternative treatments have been reported as successful in treating warts, including adhesiotherapy, hypnosis, hyperthermia, and vaccines. Perform adhesiotherapy by applying tape to the wart daily.

**Surgical Care.**Cryosurgery: Liquid nitrogen (-196$^{o}$C) is the most effective method of cryosurgery. Apply liquid nitrogen using a cotton bud applicator or cryospray to the recommended 1-2 mm rim of normal skin tissue around the wart. Repeat every 1-4 weeks for approximately 3 months, as needed. Warn patients about pain and possible blistering after treatment. Use with caution on the sides of fingers, since it can injure underlying structures and nerves. Other side effects may include scarring, ulceration, or pigment alteration. Cure rates of 50-80% have been reported. Paring the wart, in addition to 2 freeze-thaw cycles, has been a valuable adjunct to cryosurgery for plantar warts but not beneficial for hand warts.

Lasers. Carbon dioxide lasers have successfully treated resistant warts; however, the procedure can be painful and leave scarring. A risk of nosocomial infection also exists in health care workers, since HPV can be isolated in the plume.

The flashlamp-pumped pulse dye laser has shown mixed results in treating warts, with decreased risk of scarring and transmission of HPV in the smoke plume.

A study with an erbium: YAG laser revealed no HPV DNA in the smoke plume.

Electrodesiccation and curettage: Although electrodesiccation and curettage may be more effective than cryosurgery, it is painful, more likely to scar, and HPV can be isolated from the plume. Surgical excision: avoid using surgical excision in most circumstances because of the risks of scarring and recurrence.

**Prognosis.** Approximately 65% of warts disappear spontaneously within 2 years. When warts resolve on their own, no scarring is seen. However, scarring can occur as a result of different treatment methods.Treatment failures and wart recurrences are common, more so among immunocompromised patients. Normal appearing perilesional skin may harbor HPV, which helps explain recurrences.

**Patient Education.** Alert patients to the risk factors for transmission of warts. These include trauma or maceration of the skin, frequent wet work involving hands, hyperhidrosis of feet, swimming pools, and nail biting.Butchers and slaughterhouse workers also are at increased risk for developing warts.Alert patients that some warts may require more than one treatment and may be resistant to several treatment modalities. In addition, some warts may regress spontaneously without treatment.

# XIV. CONNECTIVE TISSUE DISEASES

## 14.1. Discoid Lupus Erythematosus

**Background.**Discoid lupus erythematosus (DLE) is a chronic, scarring, atrophy producing, photosensitive dermatosis. DLE may occur in patients with systemic lupus erythematosus (SLE), and some patients (<5%) with DLE progress to SLE. Some patients also have the lesions of subacute cutaneous lupus erythematosus (SCLE), and some may have a malar rash. Patients with DLE rarely fulfill 4 or more of the criteria used to classify SLE. Serologic abnormalities are uncommon. Therapy with sunscreens, topical corticosteroids, and antimalarials usually is effective.

**Pathophysiology.**DLE probably occurs in genetically predisposed individuals, but the exact genetic connection has not been determined. The pathophysiology of DLE is not well understood. It has been suggested that a heat shock protein is induced in the keratinocyte following ultraviolet (UV) light exposure or stress.

**Causes.**Patients with DLE probably have genetic predisposition; however, the precise genetic factors that increase the risk of this disease are unknown. The disease usually manifests following UV light exposure, but other triggers or inciting factors also must contribute.

**Frequency.**Worldwide, the prevalence of SLE ranges from 17-48 cases per 100,000. The highest prevalence of SLE occurs in persons aged 40-60 years, and is approximately 10 times higher in women than in men. Cutaneous lupus erythematosus (CLE) presumably occurs 2-3 times more frequently in women than in men.

**Mortality/Morbidity.**Patients with DLE rarely have clinically significant systemic disease. Lesions may produce scarring or atrophy. Scarring alopecia is particularly disturbing.

**Age.**DLE may occur at any age but most often occurs in persons aged 20-40 years. The mean age is approximately 38 years.

**History.**Patients may complain of mild pruritus or occasional pain within the lesions, but most patients are asymptomatic. Approximately 5% or fewer DLE patients have accompanying systemic involvement. Arthralgia or arthritis may occur. Patients may manifest any symptom of SLE; therefore, the history should include an assessment for symptoms of pleuritis, pericarditis, neurologic involvement, and renal involvement. Several cutaneous diseases have been reported, perhaps in greater frequency, in patients with DLE.Malignant degeneration of chronic lesions of lupus erythematosus (LE) is possible, although rare, leading to non-melanoma skin cancer. Dark-skinned individuals may be more prone to skin cancer because of the lack of pigmentation within the chronic lesion, combined with chronic inflammation and continued sun damage.Mucin deposition is a factor in the histopathology of LE. Some patients develop such a massive amount of mucin that lesions become raised and assume a different

morphology.Porphyria cutanea tarda appears to be overrepresented in LE patients. Often, the porphyria is discovered when antimalarials first are administered.
Lichen planus-like lesions may be part of an overlap between LE and lichen planus or may occur as a result of antimalarial therapy.Psoriasis is a common disease, although it is not clear whether it is more common in LE patients.
**Physical.**DLE lesions frequently are characteristic. The primary lesion is an erythematous papule or plaque with slight-to-moderate scaling. As the lesion progresses, the scale may thicken and become adherent, and pigmentary changes may develop, with hypopigmentation in the central or inactive area and hyperpigmentation at the active border. Lesions spread centrifugally and may merge. As lesions age, dilation of follicular openings occurs with a keratinous plug, termed follicular plugging or patulous follicles. Resolution of the active lesion results in atrophy and scarring. At any time, individual lesions may have any or all of these features. Early lesions may be difficult to distinguish from SCLE. DLE lesions often are photodistributed, but relatively unexposed skin also may be affected. The scalp is a common area of involvement, and permanent alopecia may result. Patients with DLE often are divided into 2 subsets: localized and widespread. Localized DLE occurs when the head and neck only are affected, while widespread DLE occurs when other areas are affected, regardless of whether disease of the head and neck is seen. Patients with widespread involvement often have hematologic and serologic abnormalities, are more likely to develop SLE, and are more difficult to treat.Several unusual variants of chronic CLE, other than DLE, have been reported.
Mucosal surfaces may be affected by lesions that appear identical to DLE of the skin or by lesions that may simulate lichen planus.Palms and soles may be affected, but this occurs in fewer than 2% of patients.DLE lesions may become hypertrophic or verrucous. This subset is manifested by wart-like lesions, most often on the extensor arms. Hypertrophic lesions of LE must be differentiated from warts, keratoacanthomas, or squamous cell carcinoma. These lesions are more difficult to treat.Lupus panniculitis is a form of chronic CLE that may be accompanied by typical DLE lesions or may occur in patients with SLE.
**Complications.**Scarring or atrophy is possible, but treatment of early lesions may be preventative.Serious systemic disease is rare, but when it occurs, patients may develop life-altering sequelae.Malignant degeneration is rare. Promptly remove new growths within burned-out lesions.
**Lab Studies.**Serologic testing.Some patients with DLE (approximately 20%) manifest a positive antinuclear antibody (ANA) when tested with human substrates. HEp-2 cells currently are the most common substrate used in commercial labs.Anti-Ro (SS-A) autoantibodies are present in approximately 1-3% of patients.Anti-native DNA (double-stranded or nDNA) or anti-Sm antibodies usually reflect SLE, and they may occur in some patients (<5%).
Other laboratory findings.Cytopenias may be present. Elevated sedimentation rate may occur in some patients. Rheumatoid factor may be positive. Complement

levels may be depressed. Urinalysis may reflect the presence of renal involvement with proteinuria.

**Other Tests.** ***Immunopathology***. Deposition of immunoglobulin and/or complement at the dermal-epidermal junction is a characteristic feature of LE referred to in most texts and articles. Tissue may be examined from skin lesions (lesional) or normal skin (non-lesional). Non-lesional biopsies may be from exposed or non-exposed surfaces. Testing of non-lesional non-exposed skin is termed the lupus band test (LBT).The use and interpretation of these tests varies according to the biopsy site. Approximately 90% of patients with DLE manifest a positive direct immunofluorescence (DIF) test on lesional skin; however, the presence of immunoreactants in the basement membrane zone of lesional skin is not specific for lupus and can be seen in a variety of inflammatory skin diseases. Older lesions or very early lesions may be more likely to be negative on immunofluorescence microscopy. Only patients with SLE have a positive LBT, defined as the presence of 4 or more immunoreactants in the basement membrane zone. LBTs are neither sensitive nor specific and mostly have been replaced by advances in serologic testing.

**Histologic Findings.**The characteristic histopathologic alterations observed in DLE include vacuolar alteration of the basal cell layer, thickening of the basement membrane, follicular plugging, hyperkeratosis, atrophy of the epidermis, incontinence of pigment, and inflammatory cell infiltrate (usually lymphocytic) in a perivascular, periappendiceal, and subepidermal location. Often, an abundance of mucin is seen within the dermis. The histopathologic features differ depending upon the type and age of the lesion.

**Medical Care.**The goals of management are to improve the patient's appearance, to control existing lesions and limit scarring, and to prevent the development of further lesions. Advise patients that the risk of serious systemic disease is possible, although rare. Regular repeat clinical evaluation accompanied by simple laboratory studies usually is sufficient to evaluate the possible progression from the primary cutaneous disorder to the disorder accompanied by systemic involvement.

Therapy begins with sun-protective measures, including sunscreens, protective clothing, and behavior alteration. Cosmetic measures, such as cover-up makeup or wigs, may be suggested for appropriately selected patients. Make-up used for camouflage includes Covermark and Dermablend.

Standard medical therapy includes corticosteroids (topical or intralesional) and antimalarials. Antimalarials appear less effective in patients who smoke; however, DLE possibly is worse in these patients. Alternative therapies include auranofin, thalidomide, oral or topical retinoids, interferon, and immunosuppressive agents.

Topical corticosteroids are selected for the type of lesion under treatment and for the site of involvement. For example, lotions or foams are preferred for the scalp, weaker agents are used on the face, and superpotent agents are used for hypertrophic lesions.

Intralesional injection of corticosteroids (typically, this author uses triamcinolone acetonide 3 mg/mL) is useful as adjunctive therapy for individual lesions. Potential

for atrophy relates to the amount of corticosteroid injected in any one area; therefore, dilute concentrations are preferred. In addition, the treating physician must take care to limit the total dose of the injections at any given office/clinic visit to avoid systemic toxicity from the steroids e.g. if a patient is given 10 mL of triamcinolone 3 mg/mL, this means that the patient has received a total of 30 mg, and toxicity is the same as if it had been delivered orally or by intramuscular injection.

Among immunosuppressives, methotrexate may be considered, although this author has observed no beneficial effects in the small number of patients treated. In this author's experience, azathioprine and, recently, mycophenolate mofetil have been successful; however, systemic corticosteroids rarely are effective.

**Surgical Care.**Excision of burned-out scarred lesions is possible; however, reactivation of inactive lesions has been reported in some patients.Laser therapy may be useful for lesions with prominent telangiectasias. Reactivation also is a consideration with this form of therapy.

**Consultations.**Rheumatology - for joint involvement.Nephrology - for renal involvement.Internal medicine - to evaluate systemic involvement.Ophthalmology - to monitor therapy with hydroxychloroquine or chloroquine.

**Activity.**Since chronic CLE is exacerbated by sunlight or other UV exposure, advise patients to take precautions, e.g. to limit exposure to sunlight to early morning or late afternoon when the sun is less intense. Advise patients to avoid artificial light sources such as tanning beds.

**Prognosis.**The prognosis of patients with chronic CLE is favorable regarding mortality; however, many patients continue to experience pain in their lesions or may experience disfigurement from the scars or atrophy that can develop.Exacerbation is possible, particularly in the spring and summer.

## 14.2. Morphea

**Synonyms and related keywords:**localized scleroderma, plaque-type morphea, generalized morphea, linear morphea, deep morphea, en coup de sabre, frontoparietal linear morphea, progressive hemifacial atrophy, atrophoderma of Pasini and Pierini.

**Background.**Morphea, also known as localized scleroderma, is a disorder characterized by thickening and induration of the skin and subcutaneous tissue due to excessive collagen deposition. Morphea subtypes are classified according to their clinical presentation and depth of tissue involvement; they include plaque-type, generalized, linear, and deep varieties. Unlike systemic sclerosis, morphea lacks features, such as sclerodactyly, Raynaud phenomenon, and internal organ involvement.

**Pathophysiology.**Overproduction of collagen by lesional fibroblasts is common to all forms of morphea, but the exact mechanism is unknown. Proposed factors involved in the pathogenesis include endothelial cell injury, immunologic and inflammatory activation, and dysregulation of collagen production. An

autoimmune etiology is supported by the frequent presence of autoantibodies in patients with morphea. Reports have shown increased levels of circulating intercellular adhesion molecule-1, which is important in immune-mediated mechanisms, and of various cytokines, such as transforming growth factor-beta, which has been shown to induce fibroblasts to reproduce features of scleroderma.

**Causes.**The cause of morphea is unknown. Investigations have not uncovered any consistent etiologic factors. Different morphea subtypes often coexist in the same patient, suggesting that the causative processes are similar.

***Radiation therapy***. Morphea may occur at the site of previous supervoltage radiation therapy for breast cancer and other cancers, developing from 1 month up to 32 years after irradiation.

***Infection or vaccination.***Infections, such as Epstein-Barr virus, varicella, measles, and borreliosis, have been reported to precede the onset of morphea and have been proposed as possible triggers.The most extensive literature focuses on *Borrelia burgdorferi* as a possible etiologic agent of morphea. Although *Borrelia* antibodies have been found in some patients and DNA from the organism has been detected in morphea lesions, a definite causal relationship has not been established.Morphealike lesions have also been reported to occur after bacillus Calmette-Guérin (BCG) and tetanus vaccinations.

***Immunologic causes***. Morphea may result from localized autoimmune reactions. Recognition of self-antigens by B cells and/or T cells may produce a local inflammatory response, ultimately resulting in the release of growth factors and other cytokines capable of stimulating fibroblast-driven overproduction of collagen. For example, transforming growth factor-beta, which may be secreted by activated T cells or tissue macrophages, has been shown to stimulate fibroblasts and endothelial cells to reproduce features of scleroderma.

***Trauma***. Trauma has been considered a possible precipitating event in morphea, but the relationship is not clear. In particular, trauma has been considered as the cause of eosinophilic fasciitis.

***Familial causes***. A few familial cases of morphea have been reported, most are of the disabling pansclerotic morphea of children subtype. No significant HLA associations have been recognized.

**Frequency.**The incidence rate of morphea has been estimated to be 27 new cases per 1 million population per year. The actual incidence of morphea may be higher because many cases may not come to medical attention due to the benign nature of morphea.

**Mortality/Morbidity.**Morphea has a benign prognosis overall, with survival rates similar to those of the general population. However, linear and deep morphea subtypes can cause considerable morbidity, especially in children when they interfere with growth. Deformities such as joint contractures, limb atrophy, and facial hemiatrophy result in substantial disability in 25-44% of patients with linear and deep morphea.

**Sex.**Women are affected about 3 times as often as men for all forms of morphea except for linear morphea, which has a more even sexual distribution.

**Age.**Linear morphea tends to affect children and adolescents, with 67% of cases occurring before age 18 years. Other morphea subtypes most often develop later in life, with a mean age of onset in persons aged 33-38 years and with 75% of cases occurring in persons aged 20-50 years.

**History.**Morphea is usually asymptomatic, and, most often, the onset of lesions is insidious, although they can occasionally develop rapidly.Arthralgias, occasionally localized to an affected extremity, are sometimes reported by patients with morphea. In patients with deep morphea, arthralgias, arthritis, and myalgias are common, and carpal tunnel syndrome may also develop.Patients with en coup de sabre lesions of linear morphea can present with seizures, headache, and visual changes.

**Physical.**Physical findings in morphea are primarily in the skin and underlying tissues, with different clinical manifestations and levels of tissue involvement in the various subtypes. Although subdivision of morphea is useful with regard to differences in epidemiology, anatomical site, and course of disease, recognizing that continuous clinical and histologic transitions exist between all the variants within the spectrum of morphea is important.

*Plaque-type morphea* is the most common and benign morphea subtype and includes guttate morphea and keloidal (nodular) morphea variants. These lesions are relatively superficial, involving only the dermis and occasionally the superficial panniculus. *Generalized morphea* is a more severe form of the disease, with widespread morphea plaques. *Linear morphea* is the most common morphea subtype in children and adolescents and includes *the en coup de sabre* and *progressive hemifacial atrophy* variants. Linear morphea often qualifies as *deep morphea* in a linear pattern, involving the deep dermis, the subcutaneous tissue, the muscle, and the underlying bone. Deep morphea, also referred to as *subcutaneous morphea* or morphea profunda, may involve the deep dermis, the subcutaneous tissue, the fascia, the muscle, and even the bone. Variants of deep morphea include eosinophilic fasciitis and disabling pansclerotic morphea of children.

***Types of skin lesions.***Morphea lesions are characterized as circumscribed indurated plaques that are 1-30 cm in diameter. They often begin as poorly defined areas of non-pitting edema, with sclerosis developing as the disease progresses. The surface becomes smooth and shiny over time, with the loss of hair follicles and the inability to sweat. Eventually, over a period of months to years, the skin softens and becomes atrophic.

Guttate morphea lesions are smaller, 2-10 mm in diameter, and superficial, with less induration and a sharply demarcated border. Guttate morphea frequently coexists with and may look similar to lichen sclerosus et atrophicus; some authors believe that the 2 disorders are related or identical.

Keloidal (nodular) morphea is a rare variant characterized by nodules resembling keloids in the presence of typical plaque-type morphea.

Atrophoderma of Pasini and Pierini may represent an end-stage (burnt-out) form of plaque-type morphea. It is characterized by atrophic plaques with well-defined cliff-drop borders, without marked inflammation or sclerosis.

Bullous morphea is a rare variant characterized by tense subepidermal bullae in the presence of plaque-type, linear, or deep morphea.
Linear morphea is characterized by discrete indurated linear bands. Melorheostosis, a dense linear cortical hyperostosis, occurs rarely in affected limbs, and calcinosis has been reported to develop within linear lesions.
Frontoparietal linear morphea, called en coup de sabre, is characterized by a linear, atrophic depression suggestive of a stroke from a sword. The lesion may be extensive and can even cause hemifacial atrophy.
Progressive hemifacial atrophy (Parry-Romberg syndrome) may be a form of linear morphea. However, unlike en coup de sabre, the primary lesion occurs in the subcutaneous tissue, the muscle, and the bone; the dermis is affected only secondarily, and the skin is not sclerotic or bound down.
Deep morphea is characterized by deep, bound-down, sclerotic plaques.
Eosinophilic fasciitis (Shulman syndrome) involves primarily the fascia and is characterized by acute onset of painful, indurated skin with a cobblestone appearance and taut swelling of the entire affected extremity caused by increased subfascial pressure. A negative vein sign (veins do not protrude normally but instead are represented by linear depressions) is typical.
Disabling pansclerotic morphea of children has generalized involvement that extends throughout the tissues from dermis to bone.
***Color of skin lesions.***Plaque-type morphea often begins as an area of erythema. In early active phases of the disease, a violaceous border (lilac ring) often surrounds the indurated area. With disease progression, the center of the lesion gradually develops a waxy, ivory color. As lesions eventually involute, an area of hypopigmentation and/or hyperpigmentation often remains. In the guttate morphea variant, lesions are typically chalk-white or silvery in color. The plaques of atrophoderma of Pasini and Pierini are hyperpigmented. In generalized morphea, often a silvery color or hyperpigmentation of the involved areas is present. Deep morphea lesions are frequently hyperpigmented, but, because of the deeper level of inflammation, they lack the color changes typical of plaque-type morphea.
***Shape of skin lesions.***Plaque-type morphea lesions are typically oval or (less often) round in shape. Linear morphea occurs as a linear band. Deep morphea lesions are rather ill defined.
***Palpation of skin lesions.***Morphea lesions are typically indurated and hard, but guttate morphea lesions are less firm. In linear and deep morphea lesions, fixation to underlying structures and extension down to involve muscle or even bone are present.
***Arrangement of skin lesions.***Plaque-type morphea lesions are most often single or few in number, although they may be multiple. Oval plaques on the trunk are typically oriented with their long axes in a horizontal, rather than vertical, direction. When bilateral, lesions are generally asymmetrical. Guttate morphea lesions are multiple. Linear morphea lesions are most often single and unilateral in 95% of cases. If both the upper extremities and the lower extremities are involved, lesions are usually homolateral. The distribution pattern of linear morphea is

controversial. Although linear morphea following the lines of Blaschko has been described in several recent reports, some authors have stated that it probably does not follow the lines of Blaschko; other authors have noted that linear morphea may appear to be dermatomal in distribution. Usually, linear morphea lesions occur along the length of a limb, but sometimes a band surrounds a limb or a finger, resembling ainhum. Deep morphea is characterized by diffuse thickening of tissues. Distribution of lesions is often symmetric.

***Areas of distribution.***Plaque-type morphea is more common on the trunk than on the extremities, and the face is usually spared. Guttate morphea primarily involves the neck and the upper part of the trunk. Atrophoderma of Pasini and Pierini usually occurs on the back. Generalized morphea occurs when morphea plaques become confluent or multiply and affect a significant portion of 3 or more major anatomical regions, often involving the upper part of the trunk, the abdomen, the buttocks, and the thighs. In a rare variant of almost universal morphea, the whole body, from the top of the head to the feet, is involved; unlike diffuse systemic scleroderma, patients lack features, such as sclerodactyly or Raynaud phenomenon. Linear morphea most often affects the lower extremities, followed in frequency of occurrence by the upper extremities, the frontal part of the head, the anterior part of the thorax, the abdomen, and the buttocks. En coup de sabre is a variant that affects the frontoparietal part of the face or the scalp, most often the paramedian part of the forehead. The occurrence of linear morphea on the extremities and the head, where the deep fascia is closer to the dermis than on the trunk, probably explains the tendency of linear morphea to affect deep structures. Eosinophilic fasciitis commonly occurs on 1 or more extremities proximal to the hands and feet. Disabling pansclerotic morphea of children begins with the extensor extremities and progresses to involve the trunk, the flexor extremities, the face, and the scalp, with sparing of the fingertips and the toes.

***Hair and nails.***Scalp involvement results in scarring alopecia, as seen in the variant known as en coup de sabre. Loss of eyebrows or eyelashes may also occur in this variant. Nail dystrophy may occur in linear lesions located on an extremity or in pansclerotic morphea.

***General examination.***Extensive truncal morphea may result in restricted respiration.When linear or deep morphea lesions cross the joint lines, they can result in restricted mobility, contractures, and deformity. In children, lesions can result in growth impairment and severe atrophy of involved limbs. Signs of carpal tunnel syndrome may be evident in patients with deep morphea (especially eosinophilic fasciitis).Linear scleroderma may also be associated with vertebral column anomalies, particularly spina bifida occulta and scoliosis.Patients with en coup de sabre may develop ptosis, ocular muscle dysfunction, uveitis, asymmetry of the tongue, and altered dentition.

**Complications.**In the linear and deep morphea subtypes, joint contractures, subcutaneous atrophy, and growth failure can be deforming and disabling.

**Lab Studies.*No diagnostic laboratory tests are available for morphea*. *CBC count***. The CBC count is most often in the reference range. Eosinophilia has been

found to correlate with disease activity in patients with linear and generalized morphea (although this is not a consistent finding) as well as in patients with eosinophilic fasciitis and other variants of deep morphea.Eosinophilic fasciitis has been associated with anemia and thrombocytopenia.

***Erythrocyte sedimentation rate***: This rate is usually in the reference range, but it may be elevated in eosinophilic fasciitis.

***Immunoglobulin G and immunoglobulin M***: polyclonal increases may occur, especially with linear and deep morphea. This finding is correlated with disease activity and the development of joint contractures in linear morphea.

***Rheumatoid factor***: this factor is positive in 25-41% of patients, especially children with linear morphea; titers are correlated with disease severity.

***Autoantibodies*** (Detection of serum autoantibodies is common in all types of morphea). Antinuclear antibody (ANA) test results are positive in 50% of patients with plaque-type or generalized morphea and in 67% of those with linear morphea, usually with a homogeneous staining pattern.Anti–single-stranded DNA antibody test results are positive in 27% of patients with plaque-type morphea, in 75% of those with generalized morphea, and in 53% of those with linear morphea; levels are correlated with extensive, active disease and joint contractures.Antihistone antibodies test results are positive in 42% of patients with morphea and in 87% of those with generalized morphea, correlating with the number of plaque-type lesions and the total area affected; levels are not correlated with the presence or the number of linear lesions.Anticentromere, anti-Scl70, and anti–double-stranded DNA antibodies are usually absent, although anticentromere antibodies were found in 12% of patients with morphea in one study.***Soluble Il-2 receptors***: levels may be correlated with disease activity.

**Imaging Studies.**Radiography may be helpful in selected cases of linear or deep morphea where bone involvement is suspected. It may also be helpful in monitoring pediatric patients sequentially for potential growth defects.MRI has been reported to be useful in diagnosing eosinophilic fasciitis and possibly for monitoring the effectiveness of therapy; however, the considerable expense makes its routine use impractical.B-mode ultrasonography can measure the skin's thickness, which may be correlated with disease activity.

**Procedures.**Although diagnosis of morphea can frequently be made based on the clinical findings, a biopsy is often useful to confirm the diagnosis and to differentiate among the subtypes.For plaque-type and generalized morphea, a deep punch biopsy is usually sufficient.For linear and deep morphea, an incisional biopsy extending down to muscle is needed.

**Histologic Findings.**Cutaneous histologic findings are similar among the morphea subtypes and systemic sclerosis, with homogenization of collagen bundles as the fundamental process. The depth of involvement is important for subdivision into the morphea subtypes. The epidermis can be either normal or atrophic with loss of rete ridges. In the early inflammatory stage, a lymphohistiocytic infiltrate, perivascular or diffuse, is often present in the reticular dermis and the fibrous trabeculae of the subcutaneous tissues; large numbers of plasma cells may also be

present. The dermis is typically edematous, with collagen bundle swelling in the lower reticular dermis. In the late sclerotic stage, the inflammatory infiltrate frequently disappears. Collagen bundles become thick, dense, homogenous, and eosinophilic, with collagen changes extending to the upper dermis and possibly also involving the panniculus, the fascia, and the muscle. Hair follicles, sweat glands, and subcutaneous fat are progressively lost as collagenous material accumulates. Direct immunofluorescence microscopy is positive in about one third of cases, most frequently with deep morphea.

**Medical Care.**No proven effective treatments for morphea exist. Most patients with plaque-type morphea experience very gradual (e.g. over 3-5 y) spontaneous remission. Therapy with topical or intralesional corticosteroids offers little or limited benefit. Treatment with topical calcipotriene may be attempted.Patients with generalized, linear, and deep morphea may require more aggressive therapy. Physical therapy to preserve range of motion is of utmost importance. Numerous therapeutic agents have been used, including systemic corticosteroids, antimalarial agents, D-penicillamine, and other anti-inflammatory and immunosuppressive agents. However, no large randomized studies of these agents in patients with morphea exist.The use of low-dose UV-A phototherapy has produced marked clinical improvement of treated morphea lesions. PUVA bath photochemotherapy has also been reported to be helpful in patients with plaque-type or linear morphea, and PUVA is considered to be one of the best treatment options available.Severe cases of morphea with elevated ANA and other autoantibody levels have been improved with the use of plasmapheresis.

**Consultations.**Referral to a dermatologist is useful to verify the diagnosis and to consider treatment measures if involvement of the plaque-type morphea is extensive. For the other morphea subtypes, referral to dermatologist is generally indicated.

**Prognosis.**Plaque-type morphea is a self-limited condition that tends to slowly involute with time; the duration of disease activity is on average 3-5 years, although it may last as long as 25 years.Linear lesions tend to persist for longer than plaque lesions, but often improve over the years. However, linear morphea, especially the en coup de sabre subtype, may remit and reactivate, remain unchanged, or become more extensive with time. In addition, patients with linear lesions may develop limb atrophy and contractures that result in limited movement and persistent disability.Disabling pansclerotic morphea of children is a rare, aggressive, and mutilating variant of deep morphea that begins before the age of 14 years and has a disease course of relentless progression and severe disability.

# XV. DISEASES OF THE ADNEXA

## 15.1. Acne Vulgaris

**Background.**Acne vulgaris is a common skin disease that affects 85-100% of people at some time during their lives. It is characterized by non-inflammatory follicular papules or comedones and by inflammatory papules, pustules, and nodules in its more severe forms. Acne vulgaris affects the areas of skin with the densest population of sebaceous follicles; these areas include the face, the upper part of the chest, and the back.

**Pathophysiology.**The pathogenesis of acne vulgaris is multifactorial. Four key factors are responsible for the development of an acne lesion: follicular epidermal hyperproliferation and hyperkeratinization, excess sebum, *Propionibacterium acnes,* and inflammation. Follicular epidermal hyperproliferation and hyperkeratinization appears to be one of the primary events in the development of an acne lesion. The follicular epidermis is hyperproliferative; abnormal production of keratins 6 and 16 could play a role. Increasing levels of the adrenally derived androgen dehydroepiandrosterone sulfate (DHEAS) are correlated with the development of the microcomedo, the primary acne lesion; therefore, these levels may trigger follicular epidermal hyperproliferation. This hyperproliferation may also be stimulated by an alteration in sebum and lipid levels in acne lesions. For example, linoleic acid levels are decreased in acne lesions, and the levels normalize after successful treatment with isotretinoin.

Excess sebum is also a key factor in the development of acne vulgaris. The amount of sebum produced and the degree and the severity of the acne are strongly correlated. Sebum excretion is under hormonal control. Androgens stimulate sebocyte differentiation and sebum production, whereas estrogens have an inhibitory effect. Sebocytes have nuclear androgen receptors. They also have 5 alpha reductase enzymes that convert testosterone to the more potent dihydrotestosterone. The androgen hormones bind their nuclear receptors and stimulate terminal sebocyte differentiation and the production of sebum. Most men and women with acne have normal circulating levels of androgen hormones. An end-organ hyperresponsiveness to androgens has been hypothesized.

*P. acnes* is a microaerophilic organism present in many acne lesions. Although, it has not been shown to be present in the earliest lesions of acne, the microcomedo, its presence in later lesions is almost certain. *P. acnes* stimulates inflammation by producing proinflammatory mediators that diffuse through the follicle wall. Recent studies have shown that *P. acnes* binds to the toll-like receptor on monocytes and neutrophils. Binding of the toll-like receptor then leads to the production of multiple proinflammatory cytokines, including interleukin 12 (IL-12), interleukin 8 (IL-8), and tumor necrosis factor (TNF). Hypersensitivity to *P. acnes* may also explain why some individuals develop inflammatory acne vulgaris.

Inflammation may be a primary phenomenon or a secondary phenomenon. Most of the evidence to date suggests a secondary inflammatory response to *P acnes* as mentioned above. However, IL-1β expression has been identified in the microcomedone, and it may play a role in the development of acne.

**Age.**Acne vulgaris may be present in the first few weeks and months of life when a newborn is still under the influence of maternal hormones. This acne resolves but may recur at the time of adrenarche when androgen hormone levels begin to rise.

**History.**Local symptoms may include pain or tenderness.Systemic symptoms are most often absent in acne vulgaris.Severe acne with associated systemic signs and symptoms is referred to as acne fulminans.Acne may have a psychological impact on any patient, regardless of the severity or the grade of the disease.

**Physical.**Acne vulgaris is characterized by comedones, papules, pustules, and nodules in a sebaceous distribution. The face may be the only involved skin surface, but the chest, the back, and the upper arms are often involved. In comedonal acne, no inflammatory lesions are present. Mild inflammatory acne is characterized by inflammatory papules and comedones.Moderate inflammatory acne has comedones, inflammatory papules, and pustules.Nodulocystic acne is characterized by comedones, inflammatory lesions, and large nodules greater than 5 mm in diameter. Scarring is often evident.

**Cause.**An external cause is seldom identifiable in acne vulgaris. Some cosmetic agents and hair pomades may worsen acne. Medications that can promote acne include steroids, lithium, some antiepileptics, and iodides.Congenital adrenal hyperplasia, polycystic ovary syndrome, and other endocrine disorders with excess androgens may trigger the development of acne vulgaris.Acne vulgaris may also be influenced by genetic factors.

**Lab Studies.**The diagnosis of acne vulgaris is a clinical diagnosis. In a female patient with dysmenorrhea or hirsutism, a hormonal evaluation should be considered. Patients with evidence of virilization should have total testosterone and DHEAS levels assessed. Patients with evidence of Cushing disease should have a 24-hour urine cortisol determination.In female patients with anovulation and hyperandrogenism, polycystic ovarian syndrome is likely. Laboratory studies in this condition should include an assessment of serum lipid levels.Skin lesion cultures to rule out gram-negative folliculitis are warranted when no response to treatment occurs or when improvement is not maintained.

**Histologic Findings.**The microcomedo is characterized by a dilated follicle with a plug of loosely arranged keratin. With progression of the disease, the follicular opening becomes dilated, and an open comedo results. The follicular wall thins, and it may rupture. Inflammation and bacteria may be evident, with or without follicular rupture. Follicular rupture is accompanied by a foreign body reaction. Dense inflammation into and throughout the dermis may be associated with fibrosis and scarring.

**Medical Care.**Treatment should be directed toward the known pathogenic factors involved in acne. These include follicular hyperproliferation, excess sebum, *P. acnes,* and inflammation. The grade and the severity of the acne help in

determining which of the following treatments, alone or in combination, is most appropriate.

***Topical treatments.****Topical retinoids* are comedolytic and anti-inflammatory. They cause epidermal differentiation and, thus, normalize follicular hyperproliferation and hyperkeratinization. Topical retinoids reduce the numbers of microcomedones, comedones, and inflammatory lesions. They may be used alone or in combination with other acne medications. The most commonly prescribed topical retinoids include adapalene, tazarotene, and tretinoin. These retinoids should be applied once daily to clean, dry skin, but they may need to be applied less frequently if irritation occurs. Skin irritation with peeling and redness may be associated with the use of topical retinoids. The use of mild, nondrying cleansers and non-comedogenic moisturizers may help reduce this irritation. Alternate-day dosing may be used if irritation persists. Topical retinoids thin the stratum corneum, and they have been associated with sun sensitivity. Instruct patients about sun protection.

*Topical antibiotics* are mainly used for their role against *P. acnes.* They may also have anti-inflammatory properties. Topical antibiotics are not comedolytic, and bacterial resistance may develop to any of these agents. The development of resistance is lessened if topical antibiotics are used in combination with benzoyl peroxide. Commonly prescribed topical antibiotics include erythromycin and clindamycin alone or in combination with benzoyl peroxide. Clindamycin and erythromycin are available in a variety of topical agents. They may be applied once or twice a day. Gels and solutions may be more irritating than creams or lotions.

*Benzoyl peroxide* products are also effective against *P. acnes,* and bacterial resistance to benzoyl peroxide has not been reported. Benzoyl peroxides are available over the counter and by prescription in a variety of topical forms, including soaps, washes, lotions, creams, and gels. Benzoyl peroxides may be used once or twice a day. These agents may cause a true allergic contact dermatitis. More often, an irritant contact dermatitis develops especially if used with tretinoin or when accompanied by aggressive washing methods.

***Systemic treatments.****Systemic antibiotics* are a mainstay in the treatment of acne vulgaris. These agents have anti-inflammatory properties, and they are effective against *P. acnes.* The tetracycline group of antibiotics is commonly prescribed for acne. The more lipophilic antibiotics, such as minocycline, are generally more effective than tetracycline. Greater efficacy may also be due to less *P acnes* resistance to minocycline. However, *P. acnes* resistance is becoming more common with all classes of antibiotics currently used to treat acne vulgaris. *P. acnes* resistance to erythromycin has greatly reduced its usefulness in the treatment of acne. Other antibiotics, including trimethoprim, alone or in combination with sulfamethoxazole, and azithromycin, are reportedly helpful. Bacterial resistance to these systemic agents may be reduced by combining them with topical retinoids and/or topical benzoyl peroxide. Prescribing different topical and systemic antibiotics may predispose to antibiotic resistance.

Some *hormonal therapies* may be effective in the treatment of acne vulgaris. *Oral contraceptives* increase sex hormone binding globulin, resulting in an overall decrease in circulating free testosterone. Combination birth control pills have shown efficacy in the treatment of acne vulgaris. Spironolactone may also be used in the treatment of acne vulgaris. Spironolactone binds the androgen receptor and reduces androgen production. Adverse effects include dizziness, breast tenderness, and dysmenorrhea. Dysmenorrhea may be lessened by coadministration with an oral contraceptive. Periodic evaluation of blood pressure and potassium levels is appropriate. Pregnancy must be avoided while on spironolactone because of the risk of feminization of the male fetus.

Isotretinoin is a *systemic retinoid* that is highly effective in the treatment of severe, recalcitrant acne vulgaris. It causes normalization of epidermal differentiation, depresses sebum excretion by 70%, is anti-inflammatory, and even reduces the presence of *P. acnes*. Isotretinoin therapy should be initiated at a dose of 0.5 mg/kg/d for 4 weeks and increased as tolerated until a cumulative dose of 120-150 mg/kg is achieved. An alternate regimen is 1 mg/kg/d for 20 weeks. Coadministration with steroids at the onset of therapy may be useful in severe cases. Isotretinoin is a teratogen, and pregnancy must be avoided. Contraception counseling is mandatory, and 2 negative pregnancy test results are required prior to the initiation of therapy. Baseline laboratory examination should also include cholesterol and triglyceride assessment and a complete blood count. Pregnancy tests should be repeated monthly, and other laboratory tests should be rechecked after 6-8 weeks of therapy. Associated mood changes and depression during treatment have been reported. Although the cause is not clear, patients should be informed of this potential effect.

The patient is considered at high risk for abnormal healing and development of excessive granulation tissue following procedures. Many dermatologists delay elective procedures, such as dermabrasion or laser resurfacing, for up to a year after completion of therapy. Other procedures to be avoided during therapy include tattoos, piercings, leg waxing, and other epilation procedures.

**Prognosis.**In male patients, acne generally clears by early adulthood. Female patients frequently have adult acne. The overall prognosis for persons with acne is good. However, acne can result in long-lasting psychosocial impairment and physical scarring.

## 15. 2. Rosacea

**Background.**Rosacea is a common condition characterized by symptoms of facial flushing and a spectrum of clinical signs, including erythema, telangiectasia, coarseness of skin, and an inflammatory papulopustular eruption resembling acne.

**Pathophysiology.**Rosacea affects the central flush/blush areas of the face (i.e. forehead, nose, cheeks, chin), although ocular disease and extrafacial lesions are well-recognized features. Vascular lability, manifested clinically as intermittent

facial flushing, is a central feature of the disease, probably related to the local release of vasoactive substances. A number of dietary triggers (e.g. hot drinks, alcohol, spicy foods) and environmental triggers (e.g. temperature changes) are well recognized. Permanent telangiectasia may result.

Sebaceous hyperplasia, fibrosis, and lymphedema characterize more severe forms of the disease. An etiologic role has been proposed for *Demodex* species (mites that normally inhabit human hair follicles). Demodectic folliculitis and blepharitis have been described, and *Demodex* mites appear in greater numbers in persons with rosacea, but evidence for a central role in the pathogenesis of rosacea is lacking. Unlike acne, seborrhea is not a prominent feature, and the pathogenesis of the inflammatory papules and pustules is not clear.

**History.**Patients are likely to have a background of facial flushing, often dating to childhood or the early teens. In adult life, flushing may be increasingly precipitated by hot drinks, heat, emotion, and other causes of rapid body temperature changes. Some patients report flushing with alcohol, which is not specific.The symptoms are usually intermittent but can progressively lead to permanently flushed skin. The latter may be described as high color and is associated with the development of permanent telangiectasia.A few individuals report a gritty quality of the eyes and facial edema.

**Physical.**The disease consists of a spectrum of symptoms and signs, with most patients failing to develop every stage of disease. Variable erythema and telangiectasia are seen over the cheeks and the forehead. Inflammatory papules and pustules may be predominantly observed over the nose, the forehead, and the cheeks. Extrafacial involvement uncommonly occurs over the neck and the upper part of the chest. Prominence of sebaceous glands may be noted with the development of thickened and disfigured noses (rhinophyma) in extreme cases. Unlike acne, patients generally do not report greasiness of the skin; instead, they may experience drying and peeling. The absence of comedones is another helpful distinguishing feature. Ocular lymphoedema may be prominent but is mostly uncommon. The condition generally does not produce scarring. Rhinophyma may occur as an isolated entity without other symptoms or signs of rosacea. It can be disfiguring and therefore distressing for patients. Some authorities consider rhinophyma to represent a different disease process.Lymphoedema may be marked periorbitally, and, on occasion, it is the presenting complaint.Symptoms of ocular rosacea may be accompanied by conjunctival injection, and rarely, chalazion and episcleritis may occur.Rosacea fulminans (pyoderma faciale) is fortunately a rare complication manifested by the development of nodules and abscesses with sinus tract formation accompanied by systemic signs.Both seborrhea and seborrheic dermatitis/blepharitis are not uncommonly observed in patients with rosacea. The reasons for these associations are not well understood.A rare caseating granulomatous variant of rosacea (acne agminata/lupus miliaris disseminatus faciei) can present with inflammatory erythematous or flesh-colored papules distributed symmetrically across the upper part of the face, particularly around the eyes and the nose. The lesions tend to be discrete, and surrounding erythema is not

a marked feature but may be present. This pattern of rosacea is sometimes associated with scarring and may be resistant to conventional treatment.

**Complications.**Rosacea keratitis and keratoconjunctivitis sicca are recognized complications.Rosacea fulminans is a rare complication. Scarring generally does not occur.

**Procedures.**A skin biopsy is sometimes performed to exclude diseases, such as lupus or sarcoidosis.

**Histologic Findings.**The histologic features of rosacea depend on the stage of disease. Non-pustular lesions show a nonspecific perivascular and perifollicular lymphohistiocytic infiltrate, accompanied by occasional multinucleated cells, plasma cells, neutrophils, and eosinophils. Papulopustular lesions show more pronounced granulomatous inflammation and sometimes perifollicular abscesses. *Demodex* folliculorum may be abundant in nearby follicles. The histologic features of acne agminata are striking, demonstrating caseating granulomata with negative stains for mycobacteria and fungi.

**Medical Care.**Systemic tetracycline in doses ranging from 250 mg daily to 500 mg tid is usually effective in treating acneiform lesions, with improvement evident within 2-4 months after commencement of therapy. Tetracycline should generally be taken on an empty stomach with water only. Tetracyclines can produce esophageal irritation and ulceration, and bedtime doses should be avoided, especially in patients with gastroesophageal reflux. Alternatives include erythromycin 500 mg bid, minocycline 50-100 mg, or doxycycline 50-100 mg daily to bid. Erythema responds poorly. Empirical trials of medication may reveal spontaneous remission after 18-36 months. The condition takes a chronic course in many individuals.Topical metronidazole is helpful for mild disease and as adjuvant to systemic therapy.Topical and systemic corticosteroids are relatively *contraindicated*, except as a short course in rosacea fulminans. Flares of rosacea or a rosacea-like dermatitis are commonly seen in patients who have been applying potent topical corticosteroids to facial skin. Topical keratolytics (e.g. benzoyl peroxide, azelaic acid) offer limited symptomatic control of inflammatory pustules. Courses of isotretinoin (0.5-1 mg/kg/d) for 4 months may be helpful for recalcitrant disease, but recurrence is common. Long-term, low-dose isotretinoin therapy may be suitable for selected patients. Isotretinoin is teratogenic and has adverse effects on serum lipid profiles. Ocular rosacea may respond to topical fusidic acid or systemic tetracycline for at least 3 months. Some patients find that regular facial massage reduces lymphoedema. Rosacea fulminans is treated with moderately high doses of prednisolone (30-60 mg daily) followed by oral isotretinoin.

**Surgical Care.**Permanent telangiectasia may be treated by electrosurgery or the 585-nm pulsed dye laser. However, facial erythema is not improved, and new telangiectases develop with the passage of time. Cosmetic improvement of rhinophyma may be produced by mechanical dermabrasion, carbon dioxide laser peel, and surgical shave techniques.

**Prognosis.**In most patients who receive treatment, a stable state is reached with variable residual symptomatology.The disease takes a chronic relapsing or progressive course for some patients.
**Patient Education.**Patients should be advised to avoid known exacerbating factors, such as hot drinks, alcohol, and extremes of temperature, and they should be encouraged to use a non-comedogenic, high-factor sunscreen when exposed to sunlight and wind.

## 15.3. Alopecia Areata

**Background.**Alopecia areata (AA) is a recurrent non-scarring type of hair loss that can affect any hair-bearing area. Clinically, AA can present with many different patterns. Although medically benign, AA can cause tremendous emotional and psychosocial stress in affected patients and their families.
**Pathophysiology.**The pathophysiology of alopecia areata remains unknown. The most widely accepted hypothesis is that AA is a T-cell mediated autoimmune condition that is most likely to occur in genetically predisposed individuals.
**Autoimmunity.** Much evidence supports the hypothesis that AA is an autoimmune condition. The process appears to be T-cell mediated, but antibodies directed to hair follicle structures also have been found in AA patients with increased frequency compared to control subjects. Using immunofluorescence, antibodies to anagen phase hair follicles were found in as many as 90% of patients with AA compared to fewer than 37% of control subjects. The autoantibody response is heterogeneous and targets multiple structures of the anagen phase hair follicle. The outer root sheath is the structure targeted most frequently, followed by the inner root sheath, the matrix, and the hair shaft. Whether these antibodies play a direct role in the pathogenesis or whether they are an epiphenomenon is not known yet.
Histologically, lesional biopsies of AA show a perifollicular lymphocytic infiltrate around anagen phase hair follicles. The infiltrate consists mostly of T-helper cells and, to a lesser extent, T-suppressor cells. $CD4^+$ and $CD8^+$ lymphocytes likely play a prominent role because the depletion of these T-cell subtypes results in complete or partial regrowth of hair in the Dundee experimental bald rat (DEBR) model of AA. The animals subsequently lose hair again once the T-cell population is replete. The fact that not all animals experience complete regrowth suggests that other mechanisms likely are involved. Total numbers of circulating T lymphocytes have been reported with both decreased and normal levels.
Recent studies in humans also reinforce the hypothesis of autoimmunity. Studies have shown that hair regrows when affected scalp is transplanted onto SCID (severe combined immunodeficiency) mice that are devoid of immune cells. Autologous T lymphocytes isolated from affected scalp were cultured with hair follicle homogenates and autologous antigen-presenting cells. Following initial regrowth, injection of the T lymphocytes into the grafts resulted in loss of regrown hairs. Injections of autologous T lymphocytes that were not cultured with follicle homogenates did not trigger hair loss.

A similar experiment on nude (congenitally athymic) mice failed to trigger hair loss in regrown patches of AA after serum from affected patients was injected intravenously into the mice. However, the same study showed that mice injected with AA serum showed an increased deposition of immunoglobulin and complement in hair follicles of both grafted and non-grafted skin compared to mice injected with control serum, which showed no deposition.

In addition, it has been shown that AA can be induced using transfer of grafts from AA-affected mice onto normal mice. Transfer of grafts from normal mice to AA-affected mice similarly resulted in hair loss in the grafts. In conclusion, certain factors within the hair follicles, and possibly, in the surrounding milieu, trigger an autoimmune reaction. Adding or subtracting immunologic factors profoundly modifies the outcome of hair growth.

Clinical evidence favoring autoimmunity suggests that AA is associated with other autoimmune conditions, the most significant of which are thyroid diseases and vitiligo.

In conclusion, the beneficial effect of T-cell subtype depletion on hair growth, the detection of autoantibodies, the ability to transfer AA from affected animals to nonaffected animals, and the induction of remission by grafting affected areas onto immunosuppressed animals are evidence in favor of an autoimmune phenomenon.

**Genetics.** Many factors favor a genetic predisposition for AA. The frequency of positive family history for AA in affected patients has been estimated to be 10-20% compared to 1.7% in control subjects. The incidence is higher in patients with more severe disease (16-18%) compared to patients with localized AA (7-13%). Reports of AA occurring in twins also are of interest. No correlation has been found between the degree of involvement of AA and the type of AA seen in relatives.

Several genes have been studied and a large amount of research has focused on human leukocyte antigen. Two studies demonstrated that human leukocyte antigen DQ3 (DQB1*03) was found in more than 80% of patients with AA, which suggests that it can be a marker for general susceptibility to AA. The studies also found that HLA DQ7 (DQB1*0301) and human leukocyte antigen DR4 (DRB1*0401) were present significantly more in patients with alopecia totalis (AT) and alopecia universalis (AU).

Another gene of interest is the interleukin-1 receptor antagonist gene, which may correlate with disease severity. Finally, the high association of Down syndrome with AA suggests the involvement of a gene located on chromosome 21.

In summary, genetic factors are likely to play an important role in determining susceptibility and disease severity. AA is likely to be the result of polygenic defects rather than a single gene defect. The role of environmental factors in initiating or triggering the condition is yet to be determined.

**Cytokines.** Interleukin 1 and tumor necrosis factor were shown to be potent inhibitors of hair growth in vitro. Subsequent microscopic examination of these cultured hair follicles showed morphologic changes similar to those seen in AA.

**Innervation and vasculature.** Another area of interest concerns the modification of perifollicular nerves. The fact that patients with AA occasionally complain of itching or pain on affected areas raises the possibility of alterations in the peripheral nervous system. Circulating levels of the neuropeptide calcitonin gene-related peptide (CGRP) were decreased in 3 patients with AA compared to control subjects. CGRP has multiple effects on the immune system, including chemotaxis and inhibition of Langerhans cell antigen presentation and inhibition of mitogen-stimulated T-lymphocyte proliferation.

**Viral etiology.** Other hypotheses have been proposed to explain the pathophysiology of AA, but more evidence is needed to support them. AA was believed to possibly have an infectious origin, but no microbial agent has been isolated consistently in patients. Many efforts have been made to isolate cytomegalovirus, but most studies have been negative.

**Frequency.**Prevalence in the general population is 0.1-0.2%. The lifetime risk of developing AA is estimated to be 1.7%. AA is responsible for 0.7-3% of patients seen by dermatologists.

**Mortality/Morbidity:** AA is a benign condition and most patients are asymptomatic; however, it can cause emotional and psychosocial stress in affected individuals. Self-consciousness concerning personal appearance can become important. Openly addressing these issues with patients is important in helping them cope with the condition.

**Age.**AA can occur at any age from birth to the late decades of life. Congenital cases have been reported. Peak incidence appears to occur from age 15-29 years.

**History.**The natural history of AA is unpredictable. Extreme variations in duration and extent of the disease occur from patient to patient. AA most often is asymptomatic, but some patients (14%) experience a burning sensation or pruritus in the affected area.The condition usually is localized when it first appears. Of patients with AA, 80% have only a single patch, 12.5% have 2 patches, and 7.7% have multiple patches. No correlation exists between the number of patches at onset and subsequent severity.AA most often affects the scalp (66.8-95%); however, it can affect any hair-bearing area. The beard is affected in 28% (males), eyebrows in 3.8%, and extremities in 1.3% of patients (see). More than one area can be affected at once.

Localized AA: episodes of localized (<50% involvement) patchy AA usually are self-limited; spontaneous regrowth occurs in most patients within a few months, with or without treatment.Extensive AA: Extensive (>50% involvement) forms of AA are less common. AT or AU were reported to occur at some point in 7% of patients; AA involving more than 40% hair loss is seen in 11%. The proportion of patients with AT appears to decrease with every decade of life.In 30% of patients with AT, complete hair loss occurred within 6 months after onset of disease. The natural evolution of AT is unpredictable, but recurrences of AA (not necessarily AT) are expected.

**Associated conditions**. Because some of the entities associated with AA occur uncommonly in the general population, a large number of patients with AA need to

be examined to confirm whether an increased prevalence of these conditions exists among patients with AA. Unfortunately, most studies are performed on small groups; therefore, the data should be interpreted carefully.***Atopic dermatitis*** is seen in 9-26% of patients with AA. In the general population, the prevalence of atopic dermatitis in children in temperate developed countries varies from 5-20%. In adults, the prevalence decreases to 2-10%. Some authors have found atopy to be a poor prognostic factor for AA.***Vitiligo*** is seen with an incidence varying from 1.8-3% compared to 0.3% in control subjects.***Thyroid disease***: Clinically evident thyroid disease was found in 0.85% of 1700 patients with AA. The prevalence of thyroid disease determined on a clinical or laboratory basis varies among studies from 0.85-14.7%. The incidence of thyroid disease in control subjects is estimated to be 0.17-2%. The presence of microsomal antibodies is found in 3.3-16% of patients. Antibodies can be found with or without signs or symptoms of thyroid disease, but patients with positive autoantibodies have a higher incidence of functional abnormalities found on thyroid-releasing hormone tests (26% vs 2.8%). The incidence of thyroid microsomal and thyroglobulin antibodies in control subjects is 7%. Other studies have not supported these results. A study in 100 patients with AA failed to find an increased incidence of circulating autoantibodies including mitochondrial and thyroglobulin antibodies.***Collagen vascular diseases*** have been found in 0.6-2% of patients with AA, while the incidence in control subjects was 0.17%. The incidence of AA in 39 patients with lupus erythematous was 10% in a study by Werth et al, in contrast to 0.42% of general dermatologic patients.***Diabetes mellitus*** was found to be more common in control subjects (1.4%) than in patients with AA (0.4%). The occurrence of AA may protect against the appearance of insulin-dependent diabetes mellitus. However, the incidence of type I diabetes mellitus was significantly higher in relatives of patients with AA compared to the general population.***Down syndrome***: AA is seen in 6-8.8% of patients with Down syndrome, but only 0.1% of patients with AA have Down syndrome. The high frequency of AA in patients with Down syndrome suggests that a genetic linkage for AA may exist on chromosome 21.***Emotional stress and psychiatric disease***: Anxiety, personality disorders, depression, and paranoid disorders are seen with increased incidence varying from 17-22% of patients, and the lifetime prevalence of psychiatric disorders was estimated to be 74% in patients with AA. Psychiatric problems are seen in both children and adults. No association has been made between the severity of the psychiatric disorder and that of AA. Stressful life events within the 6-month period preceding episodes of AA were significantly higher in patients with AA compared to patients with androgenetic alopecia or tinea capitis. Major stress factors (e.g. death in family) were reported in 12% of patients.***Others associations***: Pernicious anemia, myasthenia gravis, ulcerative colitis, lichen planus, and *Candida* endocrinopathy syndrome also have been associated with AA in some studies.

**Precipitating factors**. A precipitating factor can be found in 15.1% of patients with AA. Major life events, febrile illnesses, drugs, pregnancy, trauma, and many other events have been reported, but no clear conclusions can be drawn. Despite

these findings, most patients with AA fail to report a triggering factor preceding episodes of hair loss.

**Causes.**The true cause of AA remains unknown. The exact role of possible factors needs to be clarified (see Pathophysiology). No known risk factors exist for AA, except positive family history.The exact role of stressful events remains unclear, but they most likely trigger a condition already present in susceptible individuals, rather than acting as the true primary cause.

**Physical.**Presence of smooth slightly erythematous (peach color) or normal-colored alopecic patches is characteristic.Presence of exclamation point hairs (i.e. hairs tapered near proximal end) is pathognomonic but is not always found.Positive pull test at the periphery of a plaque usually indicates that the disease is active, and further hair loss can be expected.Hair loss on other hair-bearing areas also favors the diagnosis. The most common presentation is the appearance of 1 or many round-to-oval denuded patches.No epidermal changes are associated with the hair loss.

AA can be classified according to its pattern. Hair loss most often is localized and patchy. Reticular pattern occurs when hair loss is more extensive and the patches coalesce.Ophiasis pattern occurs when the hair loss is localized to the sides and lower back of the scalp.Conversely, sisaipho (ophiasis spelled backwards) pattern occurs when hair loss spares the sides and back of the head.AT occurs with 100% hair loss on the scalp. AU occurs with complete loss of hair on all hair-bearing areas. AA usually is focal; however, it can be diffuse, thereby mimicking telogen effluvium (TE) or the type of androgenetic alopecia seen in women. Nail involvement is as follows: nail involvement is found in 6.8-49.4% of patients and most commonly is seen in patients with severe forms of AA.Pitting is the most common finding. Several other abnormalities have been reported (e.g. trachyonychia, Beau lines, onychorrhexis, onychomadesis, koilonychia, leukonychia, red lunulae).Fingernails predominantly are affected.

**Procedures.**Diagnosis usually can be made on clinical grounds; a scalp biopsy seldom is needed, but can be helpful when clinical diagnosis is less certain.

**Histologic Findings.**A histologic diagnosis of AA can be made when characteristic features are present. Horizontal sections usually are preferred to vertical sections, since they allow examination of multiple hair follicles at different levels. The most characteristic feature is a peribulbar lymphocytic infiltrate, which is described as appearing similar to a swarm of bees. The infiltrate often is sparse and usually involves only a few of the affected hairs in a biopsy specimen. Occasionally, no inflammation is found, which can result in diagnostic difficulties. A significant decrease in terminal hairs is associated with an increase in vellus hairs, with a ratio of 1.1:1 (normal is 7:1). Other helpful findings include pigment incontinence in the hair bulb and follicular stellae.

A shift occurs in the anagen-telogen ratio, which is not specific. The normal ratio is approximately 90% anagen phase to 10% telogen phase hair follicles; in AA, 73% of hairs were found to be in the anagen phase and 27% in the telogen phase. In long-standing cases of AA, the percentage of telogen phase hairs can approach

100%. Degenerative changes of the hair matrix can be found but are uncommon. Eosinophils may be present in fibrous tracts and near hair bulbs.

**Medical Care.**Treatment is not mandatory because the condition is benign, and spontaneous remissions and recurrences are common. Treatments used are believed to stimulate hair growth, but no evidence exists that they influence the ultimate natural course of the disease. Treatment modalities usually are considered first according to the extent of hair loss and the patient's age.

Assessment of the efficacy of a treatment must be considered with care, since the condition is highly unpredictable in presentation, evolution, and response to treatment. Little data exist regarding the natural evolution of the condition. For example, in patients with less than 40% scalp involvement, a study showed no benefit with treatment (minoxidil 1% and topical immunotherapy) over placebo. The high spontaneous remission rate makes it difficult to assess clearly the true efficacy of a therapy unless appropriate controls with placebo treatment are studied. For patients with extensive AA (>40% hair loss), little data exist on the natural evolution. The rate of spontaneous remission appears to be less than in patients with less than 40% involvement. The relapse rate is high in patients with severe forms of AA. Patients with AT/AU usually have a poorer prognosis, and treatment failure is seen in most patients with any therapy.

Since AA is believed to be an autoimmune condition, different immunomodulators have been used to treat this condition. Additional treatment options for AA include minoxidil and other treatment modalities.

***Corticosteroids.***Intralesional steroids: Few studies are available regarding the efficacy of intralesional steroids, but they are used widely in the treatment of AA. Intralesional steroids are the first-line treatment in localized conditions. Topical steroids: Fluocinolone acetonide cream 0.2% (Synalar HP) twice per day induced a satisfactory-to-excellent response in 61% of patients, which was maintained in 71% of patients. Betamethasone dipropionate cream 0.05% (Diprosone) showed similar efficacy. Treatment must be continued for a minimum of 3 months before regrowth can be expected, and maintenance therapy often is necessary.

Prednisone: the use of systemic steroids for the treatment of AA is under much debate. Some authors support a beneficial role of systemic steroids in halting the progression of AA, but many others have had poor results with this form of therapy. Some benefit was shown using minoxidil 2% solution applied twice per day following a 6-week taper of prednisone, but the relapse rate remained at a minimum of 50% at 4 months in the treated group.

***Topical immunotherapy***: Topical immunotherapy is defined as the induction and periodic elicitation of an allergic contact dermatitis by topical application of potent contact allergens. Commonly used agents for immunotherapy include squaric acid dibutylester (SADBE) and diphencyprone (DPCP). These 2 sensitizers are not present in the natural or industrial environment. Dinitrochlorobenzene (DNCB) has become less popular as a result of reports that it is mutagenic in the Ames assay (a bacterial assay). Cosmetically acceptable regrowth with topical immunotherapy in patients with severe AA (>50% involvement) varies from 22-68%. Most studies

have a success rate of 30-50%. Topical immunotherapy has been used for almost 20 years; no serious adverse effects have been reported. The mechanism of action of topical immunotherapy is unknown.

***Psoralen plus UV-A***. Many studies have been performed regarding the efficacy of psoralen plus UV-A (PUVA) in the treatment of AA, and the initial response rate varies from 20-73%. The relapse rate unfortunately is high (50-88%). Most patients relapse within a few months (mean 4-8 months) after treatment is stopped. Both systemic and topical PUVA therapies have been used. The number of treatments required for regrowth varies, but 20-40 treatments usually are sufficient in most cases. A younger age at onset, a longer duration of disease, and the presence of AT or AU appear to indicate a poorer outcome.

***Cyclosporine***. Cyclosporine has been used both topically and systemically in the treatment of AA. Topical cyclosporine has not proven to be effective in severe AA, since no patient (0 of 10) showed benefit with application of a 10% cyclosporin A (CsA) solution twice per day for 12 months.

***Minoxidil***. Minoxidil appears to be effective in the treatment of AA in patients with extensive disease (50-99% hair loss). Response rates in that group vary from 8-45%. Minoxidil was of little benefit in patients with AT/AU. The 5% solution appears to be more effective.

***Other treatment modalities***. Many other modalities have been reported to have variable response rates in small studies. These include nitrogen mustard, massage and relaxation, isoprinosine, acupuncture, and aromatherapy among others. The efficacy of these treatments needs to be demonstrated in larger placebo-controlled trials before they can be recommended.

**Prevention.**AA is highly unpredictable. No treatment is effective in preventing or halting progression of the condition. No trigger can be found to explain disease exacerbation in most patients.

**Prognosis.**The natural history of AA is unpredictable. Most patients have only a few focal areas of alopecia, and spontaneous regrowth usually occurs within 1 year.Probably, less than 10% of patients experience extensive alopecia, and less than 1% have AU.Patients with extensive long-standing conditions are less likely to experience significant long-lasting regrowth.Adverse prognosis factors include nail abnormalities, atopy, onset at a young age, and severe forms of AA.

# XVI. DISEASES OF THE VESSELS

## 16.1. Erythema Induratum (Nodular Vasculitis)

**Synonyms and related keywords:** Tuberculosis-associated erythema induratum, Erythema induratum of Bazin

**Background.**In 1861, Bazin gave the name erythema induratum to a nodular eruption that occurred on the lower legs of young women with tuberculosis. In 1945, Montgomery et al, while fully acknowledging the existence of tuberculosis-associated erythema induratum, coined the term nodular vasculitis to describe chronic inflammatory nodules of the legs that showed histopathologic changes similar to those of erythema induratum, that is, vasculitis of the larger vessels and panniculitis. Erythema induratum and nodular vasculitis had been considered the same disease entity for a long time. However, nodular vasculitis is now considered a multifactorial syndrome of lobular panniculitis in which tuberculosis may or may not be one of a multitude of etiologic components. Therefore, erythema induratum/nodular vasculitis complex is classified into 2 variants. Erythema induratum of Bazin type and nodular vasculitis or erythema induratum of Whitfield type. Bazin type is related with tuberculous origin, but Whitfield type is not.
**Pathophysiology.**The morphologic, molecular, and clinical data suggest that erythema induratum and nodular vasculitis represent a common inflammatory pathway, that is, a hypersensitivity reaction to endogenous or exogenous antigens. One such antigen is the tubercle bacillus. Patients with erythema induratum have a positive tuberculin skin test result and a marked increase in their peripheral T lymphocyte response to purified protein derivative (PPD) of tuberculin, which can cause a delayed-type hypersensitivity reaction.
**Causes.**Erythema induratum/nodular vasculitis complex is a multifactorial disorder. *Mycobacterium tuberculosis* and delayed-type hypersensitivity are considered etiologic factors for erythema induratum of Bazin type. Recently, hepatitis C virus has been suggested, but a direct relationship remains unclear. *M. tuberculosis* is the cause of erythema induratum. The cause is unknown in cases of nodular vasculitis with a negative tuberculin skin test reaction.
**Mortality/Morbidity.**To date, no fatal cases of erythema induratum have been reported. However, the chronic, recurrent, painful nodules and resultant scarring can be a source of significant morbidity.
**Sex.**Erythema induratum shows female predominance, and lower extremities are the most common sites in both male and female patients; however, it also may occur in other areas.
**Age.**Erythema induratum most commonly affects women aged 20-30 years. The condition is more common in young women than in other people, but it may occur later in life.

**History.**A past or present history of tuberculosis at an extracutaneous site occurs in about 50% of patients.Pulmonary tuberculosis is most common. Tuberculous cervical lymphadenitis is the next most common finding. Tender, erythematous nodules are present on the lower legs. The nodules have a chronic, recurrent course. The lesions heal with ulcerations or depressed scars. Leg edema may be present.

**Physical.**Crops of small, tender, erythematous nodules may be observed. Commons sites are the calves, although the shins are also sometimes involved. Uncommonly, the trunk, buttocks, thighs, and arms can be involved.The nodules are concentrated on the lower third of the legs, especially around the ankles.Lesions may ulcerate with bluish borders, which may be precipitated by cold weather. These irregular and shallow ulcerations can result in permanent scarring and hyperpigmentation of the lesions.

**Complications.**Inadequately treated or untreated erythema induratum may result in prolonged disease, persistent ulcerations, and complications due to coexistent systemic tuberculosis.

**Lab Studies.**A complete blood cell count may be performed. The erythrocyte sedimentation rate may be increased.

**Imaging Studies.**Chest radiography may be performed. Search for evidence of active or previous infection.

**Other Tests.**Polymerase chain reaction provides rapid and sensitive detection of *M. tuberculosis* in formalin-fixed, paraffin-embedded specimens. Polymerase chain reaction can be applied to differentiating nodular vasculitis from erythema induratum of Bazin because the demonstration of mycobacteria emerges as the only reliable criterion in erythema induratum of Bazin type.

**Procedures.**Some patients are highly sensitive to tuberculin PPD. Patients should be tested with a 1:10,000 dilution Mantoux test.An excisional biopsy containing adequate subcutaneous fat is recommended. Special stains for bacterial, fungal, and acid-fast organisms, as well as tissue for culture of these organisms, are generally obtained.

**Histologic Findings.**Findings consist of a mixed septal and lobular granulomatous panniculitis with neutrophilic vasculitis. Caseationl-ike necrosis may also be seen. The histologic features are not specific; they vary depending on the age of the lesion undergoing biopsy and the overlap with other forms of panniculitis. Vasculitis is not always identified and is not a requisite for the diagnosis. The presence of both septal granulomatous inflammation and lobular granulomatous inflammation is, nonetheless, characteristic of erythema induratum and contrasts with erythema nodosum (primarily septal) and polyarteritis nodosa (medium vessel vasculitis with minimal lobular inflammation).

**Medical Care.**Erythema induratum of Bazin is treated with antituberculous therapy. Antituberculosis monotherapy has been abandoned because of high resistance; a multidrug combination regimen is more widely accepted.Bed rest with systemic steroids may be indicated. Potassium iodide is sometimes applied, with

high efficacy; however, this therapy requires caution when used in children or in patients with thyroid disease.
**Prognosis.**The prognosis is good if treated properly.

## 16.2. Henoch-Schönlein Purpura (Anaphylactoid Purpura)

**Background.**Henoch-Schönlein purpura (HSP) is an immunoglobulin (Ig) A-mediated small-vessel vasculitis that predominantly affects children but also is seen in adults. HSP is a subset of necrotizing vasculitis characterized by fibrinoid destruction of blood vessels and leukocytoclasis. Clinical manifestations primarily include palpable purpura, arthralgia or arthritis, abdominal pain, gastrointestinal (GI) bleeding, and nephritis. The most serious long-term complication from HSP is progressive renal failure, which occurs in 1-2% of patients.
Heberden first described the disease in 1801 in a 5-year-old child with abdominal pain, hematuria, hematochezia, and purpura of the legs. In 1837, Johann Schönlein described a syndrome of purpura associated with joint pain and urinary precipitates in children. Eduard Henoch, a student of Schönlein's, further associated abdominal pain and renal involvement with the syndrome. Frank proposed the term "anaphylactoid purpura" in 1915. This followed from the reasoning that the pathogenesis likely involved a hypersensitivity reaction to an inciting agent.
Two major classification systems are used to make a diagnosis of HSP. The first, from the American College of Rheumatology, requires two or more of the following to be present: (1) Patient age younger than 20 years; (2) Palpable purpura; (3) Abdominal pain or GI bleeding; (4) Extravascular or perivascular granulocytes on biopsy. The second classification system is from the Chapel Hill Consensus Group, primarily uses nonclinical criteria, and requires only the presence of small-vessel vasculitis with IgA deposition.
Two additional sets of criteria have been suggested for the diagnosis of HSP. Helander et al proposed that three or more of the following be present: (1) Direct immunofluorescence (DIF) results consistent with vascular IgA deposition;(2) Patient age younger than 20 years; (3) GI involvement; (4) Upper respiratory infection tract (URI) prodrome; (5) Mesangioproliferative glomerulonephritis with or without IgA deposition. Michel et al. proposed criteria to differentiate HSP from hypersensitivity vasculitis, requiring three or more of the following be present to diagnose HSP: (1) Palpable purpura; (2) Bowel angina; (3) GI bleeding; (4) Hematuria; (5) Patient age of onset younger than 20 years; (6) No medications as a precipitating agent.
**Pathophysiology.**The etiology of HSP is unknown but involves the vascular deposition of IgA immune complexes. More specifically, the immune complexes are composed of IgA1 and IgA2 and are produced by peripheral B lymphocytes. These complexes likely are formed in response to an inciting factor. The circulating complexes become insoluble, are deposited in the walls of small vessels (arteries, capillaries, venules), and activate complement, most likely by the

alternative pathway (based on the presence of C3 and properdin and the absence of the first component of complement in most biopsies).
Polymorphonuclear leukocytes are recruited by chemotactic factors and cause inflammation and necrosis of vessel walls with concomitant thrombosis. This leads to extravasation of erythrocytes from hemorrhage in the affected organs and is manifested histologically as leukocytoclastic vasculitis.
Histology of involved skin reveals polymorphonuclear cells or cell fragments around small dermal blood vessels. Immune complexes containing IgA and C3 have been found in skin, kidneys, intestinal mucosa, and joints, which are the major organ sites involved in HSP.
Clinical manifestations of HSP reflect small-vessel injury. Abdominal pain, present in as many as 65% of patients, is secondary to vasculitis-induced submucosal and subserosal hemorrhage and edema, with thrombosis of the microvasculature in the gut. Hematuria and proteinuria occur in HSP-associated nephritis. Renal manifestations range from minimal change to severe crescentic glomerulonephritis.
Etiology is secondary to the mesangial deposition of IgA predominantly, but IgG, IgM, C3, and properdin deposition also may occur. These deposits also can occur in the subendothelial and subepithelial glomerular spaces. Many believe that both HSP nephritis and IgA nephropathy (Berger disease), which are the most common causes of glomerulonephritis in the world, are different clinical presentations of the same disease process. Dermatologic manifestations occur secondary to immune complex deposition (IgA, C3) in vessels of the papillary dermis, resulting in vessel injury, extravasation of RBCs, and clinically observable palpable purpura. This tends to occur in dependent body regions, such as the lower legs, buttocks, back, and abdomen.
As many as 50% of occurrences in pediatric patients are preceded by a URI, and a recent study in adults demonstrated that 40% of patients had an antecedent URI. Several agents have been implicated, including group A streptococci, varicella, hepatitis B, Epstein-Barr virus, parvovirus B19, *Mycoplasma*, *Campylobacter*, and *Yersinia*. Less commonly, other factors have been associated as inciting agents in the development of HSP. These include drugs, malignancy, foods, pregnancy, familial Mediterranean fever, and exposure to cold. HSP also has been reported following vaccinations for typhoid, measles, yellow fever, and cholera.
**Frequency.**In the US, 75% of HSP occurrences are in children aged 2-14 years. The incidence in this age group is 14 per 100,000 population.
**Mortality/Morbidity.**Most morbidity and mortality in this disease results from glomerulonephritis and its associated acute and chronic renal manifestations. At a minimum, transient hematuria occurs in 90% of patients. Renal insufficiency occurs in fewer than 2% of patients, and end-stage renal failure occurs in fewer than 1%. HSP accounts for 3-15% of children entering dialysis programs.
**Age.**Most patients (75%) are children aged 2-14 years. The median age of onset is 4-5 years. Although one of the criteria for the diagnosis of HSP as published by the

American College of Rheumatology is "age less than 20 years," the disease can occur from infancy to the ninth decade.

**History.**The presenting history varies with each patient. The hallmark of the disease is the characteristic palpable purpura, which is seen in almost 100% of patients. HSP tends to occur on the buttocks and upper thighs in younger children and on the feet, ankles, and lower legs of older children and adults. Patients often present with low-grade fever and malaise in addition to more specific symptoms. Purpura may be the presenting sign. As many as 50% of children present with symptoms other than purpura. The eruption often is preceded by arthralgia or arthritis, abdominal pain, or testicular swelling. Although it may be present initially, renal disease often develops up to 3 months after initial presentation.

***Joint symptoms***: Arthralgia or arthritis is the presenting complaint in 25% of patients and occurs at some point in 60-75% of patients. Ankles and knees are affected most commonly, although any joint may be involved.

***Abdominal pain***: Abdominal pain with concomitant hematochezia is the second most frequent symptom, is observed in 50-65% of patients, and is the presenting complaint in 10-15%. Pain tends to be sharp or colicky, and surgical consultation may be indicated to exclude a surgical abdomen. Indeed, as many as 6% of patients require surgery as a result of complications such as intussusception, bowel wall perforation, or infarction. Gastric hemorrhage with hematemesis, hydrops of the gallbladder, appendicitis, and pancreatitis also has been reported.

***Renal involvement.***An incidence of renal involvement of 10-60% has been reported, and the extent of glomerular injury mostly determines the long-term morbidity and mortality of HSP. The presence of glomerular crescents on renal biopsy correlates with a poor prognosis. HSP nephritis usually presents as macroscopic hematuria and proteinuria lasting days to weeks. These may be accompanied by increased plasma creatinine and/or hypertension, followed by microscopic hematuria, which may last months to years. Gross hematuria may occur years after the initial illness with relapses of purpura, often following a URI. Of those patients with renal involvement, as many as 10% may develop chronic renal failure and end-stage renal disease. However, fewer than 1% of patients with HSP suffer this poor prognosis.

***Disease recurrence***: Disease recurrence occurs throughout weeks to months in adults and children. In the large pediatric study by Allen et al, children older than 2 years had a recurrence rate of 50%, while those younger than 2 years had a less than 25% chance of recurrence. The primary differences between children and adults, according to one study of 57 adults with HSP, are the chronicity and severity of the eruption in the latter population. Bullae and ulcers are more common in adults, and cutaneous exacerbations may be seen for 6 months or longer.

***Other signs and symptoms***: Less common manifestations of HSP include testicular pain and swelling, hepatosplenomegaly, central or peripheral nervous system involvement (seizures or mononeuropathies, respectively), headache, and rarely, myocardial infarction or pulmonary hemorrhage.

**Physical.**A full physical examination is indicated, since HSP can affect many organ systems. ***Skin - The primary lesion***. An eruption may begin as erythematous macular or urticarial lesions, progressing to blanching papules, and later, to palpable purpura, usually 2-10 mm in diameter. However, bullae, vesicles, petechiae, and ecchymotic, necrotic, ulcerative, or target-ike lesions also may occur. Subcutaneous edema is common in children younger than 3 years.
***Skin – Distribution.***Lesions typically are symmetric and tend to be distributed in dependent body areas, such as the ankles and lower legs in older children and adults, and the back, buttocks, upper extremities, and upper thighs in young children, since these regions tend to be dependent in the latter group. The face, palms, soles, and mucous membranes usually are spared, except in infants, in whom facial involvement may not be uncommon. The subcutaneous edema prominent in young children involves the scalp, periorbital regions, hands, feet, and scrotal area.Lesions usually occur in crops and may fade over several days. Recurrences tend to occur in the same sites as previous lesions.
***Skin: Color*** as seen in the areas of purpura progresses from red to purple, then becomes rust-colored or brown before fading.
***Heart***: Cardiac tamponade and myocardial infarction rarely have been reported with HSP.***Lungs***: Although seldom a manifestation of HSP, pulmonary hemorrhage has been reported. When present, it is a poor prognostic sign with a 50% mortality rate. One pediatric study showed that 95% of patients with active disease had impaired diffusion capacity of carbon monoxide, which was readily reversible once the syndrome resolved.***Abdomen***: Pain secondary to vasculitic involvement of small mesenteric or bowel mucosal vessels is common. Examine the abdomen for a palpable mass, which may indicate intussusception. Pancreatitis, gallbladder hydrops, appendicitis, and massive gastric hemorrhage also have been reported.***Scrotum/testicles***: Testicular involvement has varied in reports from 4-38%. Testicular pain may be so intense that it mimics torsion.***Extremities***: Arthralgia and arthritis are common, primarily affecting the ankles and knees, although any joint may be involved. Periarticular inflammation is common.***Neurologic***: Headaches, seizures, and mononeuropathies rarely have been reported with HSP. Perform a careful neurologic examination for focal deficits.
**Complications:** Renal involvement, chronic renal failure.
**Lab Studies.*Urinalysis***: Since renal failure and end-stage renal disease are the most serious long-term sequelae of this disease, initial and repeated urinalyses (UA) are crucial for appropriate monitoring of disease progression and resolution. Proteinuria and microscopic hematuria are the most common abnormalities on UA. Since renal involvement may follow the appearance of purpura for up to 3 months, perform UA monthly for several months after presentation.***Serum electrolytes***: Creatinine and blood urea nitrogen measurements indicate HSP-associated acute or chronic renal failure. Electrolyte imbalance may exist if significant diarrhea, GI bleeding, or hematemesis is seen.***Antistreptolysin-O antibody titer***: URIs with streptococcal species have been implicated as predisposing factors in as many as 50% of patients.***Serum IgA level***: The level often is elevated in HSP, although this

is not a specific test for the disease.***Antinuclear antibody test***: Systemic lupus erythematosus is in the differential diagnosis for HSP.***Rheumatoid factor***: IgA rheumatoid factor has been reported in patients with HSP. In addition, rheumatoid arthritis is in the differential diagnosis for patients presenting with significant joint complaints.

***CBC with differential***: Perform a CBC to determine etiology when a suggestion of underlying infection exists (e.g. pandemia with bacterial infection) and to exclude thrombocytopenia as a cause of purpura.***Coagulation studies***: Perform prothrombin time (PT) and partial thromboplastin time (aPTT) to exclude a bleeding diathesis.***Liver function tests and hepatitis serologies***: Hepatitis B has been reported in association with HSP.***Direct immunofluorescence*** (DIF): Perform DIF for IgA on biopsy sections to demonstrate the predominance of IgA deposited in vessel walls of affected tissues. Perilesional skin adjacent to cutaneous lesions also may demonstrate IgA deposits. Renal biopsy specimens demonstrate mesangial IgA deposition in a granular pattern, often with C3, IgG, or IgM. This test is both sensitive and specific for HSP.***Stool culture and guaiac***: With appropriate history of GI complaints, a stool culture may be useful to search for *Yersinia* or *Campylobacter* species. Always search for occult GI bleeding when HSP is suspected.***Serum markers of inflammation***: ESR and CRP often are elevated in HSP. ***Renal biopsy***: Renal insufficiency with nephrotic range proteinuria (>3.5 g protein/24 h) justifies renal biopsy. DIF for IgA reveals granular mesangial IgA deposition.

**Imaging Studies.*Ultrasound:*** Ultrasound is indicated if abdominal pain is present to exclude intussusception, bowel wall edema, thickening, or perforation. This modality also is useful to evaluate acute testicular pain to exclude torsion.

***Chest x-ray***: Chest x-ray excludes pulmonary nodules or hilar adenopathy suggestive of malignancy (primary or metastatic) or lymphoma, which have been associated with HSP.

**Procedures.*Skin biopsy***: Biopsy early skin lesions for routine histology and DIF to confirm diagnosis or when diagnosis is in question.***Renal biopsy***: Perform renal biopsy when renal insufficiency with nephrotic range proteinuria is seen. Perform DIF for IgA deposits.***Esophagogastroduodenoscopy***: Upper GI endoscopy is indicated in patients with HSP when epigastric pain, melena, or hematemesis is present. Esophagogastroduodenoscopy (EGD) often demonstrates intensely red raised lesions, multiple ulcers, or diffuse erosive lesions. The duodenum frequently is involved.***Colonoscopy***: Colonoscopy is indicated when severe rectal bleeding exists. The appearance of the lesions is similar to that described for EGD.

**Histologic Findings.**Leukocytoclastic vasculitis is the predominant finding in affected tissues. Skin biopsy demonstrates fibrinoid necrosis of arteriolar and venular walls in the superficial dermis, with neutrophilic infiltration of the walls and perivascular regions. Associated fragments of inflammatory cells with nuclear debris are seen. Products of lysosomal enzyme digestion, as well as erythrocytes from hemorrhage, are extravasated. DIF shows IgA deposition in affected blood vessels. IgM, C3, and properdin also may be seen. Note that immune complex

deposition occurs before chemotactants attract neutrophils, which then causes vascular injury. Once necrosis occurs, immune complexes disappear.
Mucosal biopsy from affected GI tissue shows histopathology identical to that seen in the skin. Biopsy of affected renal tissue shows a spectrum of glomerular disease from minimal change to severe crescentic glomerulonephritis. IgA, C3, fibrin, properdin and to some extent IgG and IgM, are seen as granular mesangial deposits on DIF. If severe disease is present, deposits also may be seen in the subendothelial and subepithelial spaces.
**Medical Care.**HSP usually is self-limited and treatment primarily is supportive to assure adequate hydration and replace excessive blood loss. Search for and treat underlying or predisposing factors. Controversies concerning the use of corticosteroid and other therapies in the treatment of HSP exist, since no randomized, double-blind, placebo-controlled trials support their use. Some retrospective studies have shown that steroids can relieve abdominal pain and GI bleeding if administered within the first 24-48 hours. Other studies demonstrated no difference between patients treated with steroids and those treated with placebos. Some studies also have suggested that corticosteroid therapy may prevent the onset of delayed-HSP nephritis or lessen the severity of glomerular injury.
The presence of nephrotic-range proteinuria and hematuria are associated with a 15% risk of renal failure, and the presence of more than 50% glomerular crescents on renal biopsy is associated with 50% renal failure over a 10-year period. Because of the potentially severe sequelae in these patients, initiate corticosteroid therapy when nephrotic-range proteinuria with hematuria is seen or when biopsy demonstrates glomerular crescents. One uncontrolled study showed the benefit of combination therapy in severe HSP nephritis with methylprednisolone, cyclophosphamide, and dipyridamole. Dapsone, azathioprine, and IV immunoglobulin therapies have been tried with varying success, as has plasmapheresis. Non-steroidal anti-inflammatory drugs (NSAIDs) may be used to treat arthralgia associated with HSP. Oral corticosteroids may be of benefit in treating painful subcutaneous edema.
**Consultations.**Dermatology - for diagnosis when a cutaneous eruption is the presenting symptom of HSP.Gastroenterology - for possible EGD or colonoscopy when hematemesis, melena, or hematochezia is present.Surgery - for evaluation when abdominal pain is the presenting symptom and severity mimics that of an acute abdomen.Nephrology - for evaluation, diagnosis, and management of the renal complications of HSP.
**Prognosis.**Prognosis is excellent, except when progressive renal failure and end-stage renal disease develop. Perform monthly UA both in patients who have signs or symptoms of nephritis (to monitor progression versus resolution) and in patients who have no evidence of nephritis (may develop signs of renal involvement months after initial presentation).The syndrome resolves after 4-6 weeks in most patients, although as many as 50% have a recurrence.

## 16.3. Hypersensitivity Vasculitis (Leukocytoclastic Vasculitis)

**Background.**Leukocytoclastic vasculitis (LCV) is a histopathologic term commonly used to denote a small-vessel vasculitis. Many possible causes exist for this condition, but a cause is not found in as many as 50% of patients.

The disorder may be localized to the skin, or it may manifest in other organs. The internal organs most commonly affected include the gastrointestinal tract or the kidneys. Joints are also commonly affected. The prognosis is good when no internal involvement is present. The disorder may be acute or chronic.

**Pathophysiology.**In the past, circulating immune complexes were believed to cause LCV. Although immune complexes are involved in the pathogenesis of LCV, other autoantibodies cause disease manifestations, such as antineutrophil cytoplasmic antibody (ANCA), other inflammatory mediators, and local factors that involve the endothelial cells and other adhesion molecules. The exact mechanisms remain to be elucidated.

**Frequency.**Hypersensitivity vasculitis reportedly has an incidence of 10-30 cases per million people per year.

**Mortality/Morbidity.**The prognosis of LCV is generally good, but mortality is possible if the kidneys, the gastrointestinal tract, the lungs, the heart, or the central nervous system are involved. Chronic cutaneous disease may involve ulceration or painful bouts of purpura. Some patients alter their lives because of recurrent purpuric eruptions.

**Age.**LCV may occur at any age. In children, LCV may be called Henoch-Schönlein purpura. This condition may also occur in adults. Another form of vasculitis that is reported in infancy is acute hemorrhagic edema.

**History.**Patients with vasculitis of their skin may complain of itching, a burning sensation, or pain, or they may have asymptomatic lesions.Vasculitis of the skin may occur in the absence of any systemic disease. Vasculitis may manifest as an eruption only, or it may occur in conjunction with collagen vascular disorders, paraproteinemia, ingestants (drugs or foods), infections, or malignancy (rare).Elicit information about possible systemic manifestations from patients. Inquire about the presence or the absence of fever, arthralgia, arthritis, myalgia, abdominal pain, diarrhea, hematochezia, cough, hemoptysis, sinusitis, paresthesia, weakness, and hematuria.

Obtain information about symptoms of an associated disorder. Determine the patient's history of intravenous drug use, hepatitis, transfusion, and travel, along with symptoms or a history of inflammatory bowel disease and collagen vascular disorder, particularly rheumatoid arthritis, lupus erythematosus, or Sjögren syndrome.

**Physical.**Palpable purpura is the most common manifestation of cutaneous vasculitis, but other manifestations may occur. Palpable purpura is the most frequent presentation of small-vessel vasculitis. Lesions are usually round and 1-3 mm in diameter. Lesions may coalesce to form plaques; they may ulcerate in some instances.Retiform lesions were associated with immunoglobulin A (IgA)–related

immune complex disease in one study; however, this result has not been validated in subsequent studies.Palpable purpura is most frequently observed on the legs, but any surface can be involved. Purpuric lesions are sometimes barely palpable.Urticarial lesions may occur in some patients; rarely, this type of lesion can predate purpuric lesions.Urticarial lesions are of a different character than routine urticaria, tending to be of longer duration (often >24 h) and tending to resolve with some residual pigmentation or ecchymosis. Patients complain of a burning sensation rather than itching.To determine the duration of individual lesions, encircle several lesions and ask the patient to observe them periodically and note when they resolve or when they change shape and when a lesion is outside the encircled area.

Patients with hypocomplementemic urticarial vasculitis may develop chronic obstructive pulmonary disease; carefully examine the heart and the lungs.Livedo reticularis is a rare manifestation of small-vessel vasculitis. It is more frequent in patients with occlusive or inflammatory disease of medium-sized vessels.Nodular lesions may occur in some patients with small-vessel vasculitis. Ulceration is more common in vasculitis that affects larger vessels, but it may complicate intense purpura.Perform a careful physical examination in patients with vasculitis, including specific observation of cardiopulmonary, musculoskeletal, and gastrointestinal systems.

**Causes.**Between one third and one half of cutaneous vasculitis cases are idiopathic; the remainder have a variety of causes.Antibiotics are the most common drugs that can cause cutaneous vasculitis, particularly beta-lactams. Non-steroidal anti-inflammatory drugs and diuretics also frequently cause vasculitis. However, almost all drugs are potential causes.Various infections may be associated with vasculitis. Upper respiratory tract infections (particularly beta-hemolytic streptococcal infection) and viral hepatitis are most often implicated. HIV infection may also be associated with some cases of cutaneous vasculitis. Ascertaining whether a drug (e.g. antibiotic) or an infection (e.g. upper respiratory infection) is responsible for the disease is impossible because the occurrence of vasculitis postdates infection and the drug used to treat the infection.

Foods or food additives may cause vasculitis. Hepatitis C is a regularly recognized cause of vasculitis, probably through the presence of cryoglobulins. Interestingly, cryoglobulins were present in roughly 40% of those tested; many patients with cryoglobulins (98%) did not have vasculitis despite an abnormal circulating paraprotein. Hepatitis B was implicated in some cases of vasculitis in the past.Collagen vascular diseases account for 10-15% of cases of vasculitis. In particular, rheumatoid arthritis, Sjögren syndrome, and lupus erythematosus may have an associated vasculitis. The presence of vasculitis often denotes active disease and possibly a poorer prognosis.Inflammatory bowel disease, ulcerative colitis, or Crohn colitis may be associated with cutaneous vasculitis. Malignancy accounts for less than 1% of cases of cutaneous vasculitis.Perhaps lymphoproliferative diseases are more common (particularly hairy cell leukemia); however, any type of tumor at any site may possibly be related to cutaneous

vasculitis.Effective tumor therapy in some patients has led to resolution of the vasculitis.Small-vessel cutaneous vasculitis may be seen uncommonly in patients with a larger vessel vasculitis, such as Wegener granulomatosis, polyarteritis nodosa, or Churg-Strauss syndrome.

**Lab Studies.**Evaluation of patients with vasculitis serves 2 purposes: to determine the presence of systemic disease and to identify an associated disorder, which aids in predicting the patient's prognosis.No established routine exists, but testing for all adult patients includes a complete blood count, an erythrocyte sedimentation rate, a urinalysis, and a blood chemistry panel.Obtain stool guaiac or Hematest for patients with bowel symptoms even though these tests are not particularly reliable.Obtain serologic studies (e.g. antinuclear antibody, ANCA, rheumatoid factor) for patients without an obvious disease cause. In children and perhaps in some adults, serologic testing for a possible streptococcal infection should be considered (Streptozyme or ASO titer).Complement levels, including total hemolytic complement (CH100 or CH50), C3 levels, and C4 levels, may be obtained for patients suspected of having lupus erythematosus or patients who have urticarial vasculitis.Include serum protein electrophoresis, cryoglobulins, and hepatitis C antibody in tests for paraproteins for patients without otherwise identified disease.

Hepatitis B was associated with vasculitis in the past; however, it appears that the association may have occurred by virtue of co-infection with hepatitis C (previously termed non-A, non-B).The measurement of hepatitis B surface antigen may not be required in all cases.Cryoglobulins are often not obtained properly; a positive rheumatoid factor should suggest the presence of cryoglobulins.Perform HIV testing for patients at high risk for infection and possibly for those with otherwise unidentifiable cause of disease.Consider obtaining direct immunofluorescence microscopy for selected patients. The presence of IgA occurs in Henoch-Schönlein purpura.

**Imaging Studies.**Chest radiography is part of the routine evaluation. Consider performing visceral angiography for patients with a severe vasculitic syndrome.Perform cardiac ultrasonography and blood cultures for patients with fever and/or a heart murmur.

**Procedures.**Perform a skin biopsy of a relatively fresh lesion in most, if not all, adult patients. For humanitarian reasons, biopsies are often not performed in children with suspected vasculitis.Consider performing a biopsy of muscle or a biopsy of visceral organs in patients with severe vasculitic syndromes; however, most patients with leukocytoclastic vasculitis of the skin do not require such tests.Obtaining a bone marrow sample may be useful if the peripheral smear is abnormal.

**Histologic Findings.**A skin biopsy sample reveals the presence of vascular and perivascular infiltration of polymorphonuclear leukocytes with formation of nuclear dust (leukocytoclasis), extravasation of erythrocytes, and fibrinoid necrosis of the vessel walls. This process is dynamic; a biopsy sample of a lesion too early or too late in its evolution may not reveal these findings.

The picture of leukocytoclastic vasculitis is a pattern that can occur in any vasculitic syndrome but may also occur in non-vasculitic diseases (e.g. neutrophilic dermatoses), at the base of a biopsy sample of a leg ulceration, or in some insect bite reactions. Careful clinical-pathologic correlation is necessary.

**Medical Care.**Once a diagnosis of cutaneous small-vessel vasculitis is established and the patient is fully evaluated, specific or nonspecific management options may be used.Elevation of the legs or compression stockings may be useful because the disease often affects dependent areas.Treat the cause in patients with an identifiable cause. Removal of a drug thought to be causing the vasculitis may result in rapid clearing of the process in up to 2 weeks.Treat chronic disease that primarily involves the skin with nontoxic modalities whenever possible; avoid using systemic corticosteroids and/or immunosuppressive agents. Colchicine or dapsone may be administered for patients with disease of the skin with or without joint manifestations.Patients with urticarial lesions may be treated with antihistamines (both soporific ones and less sedating agents). Sometimes, a combination of these agents is needed to control disease manifestations. Some patients have responded to non-steroidal anti-inflammatory agents.Patients with severe visceral involvement may require high doses of corticosteroids (1-2 mg/kg/d) with or without an immunosuppressive agent (e.g. cyclophosphamide, azathioprine, methotrexate).

**Surgical Care.**Surgical care for patients with vasculitis is rarely needed. Surgical care may be appropriate if a tumor is identified as a cause of the process.Surgical care may be appropriate if recalcitrant ulceration occurs after control of active disease.

**Prognosis.**The prognosis of patients with cutaneous vasculitis depends on the underlying syndrome or the presence of end-organ dysfunction.Patients with disease that primarily affects the skin and/or the joints have a good prognosis.Patients with Wegener granulomatosis, polyarteritis nodosa, Churg-Strauss syndrome, or severe necrotizing vasculitis have a potentially fatal disease. Treatments with corticosteroids and/or immunosuppressive/cytotoxic agents often save the patient's life.

## 16.4. Kaposi Sarcoma

**Background:** In 1872, Moritz Kaposi (1837-1902) of Kaposvar, Hungary, a dermatology faculty member at the University of Vienna, first described *idiopathisches multiples Pigmentsarkom der Haut*, which has become known as Kaposi sarcoma (KS). KS had brownish red–to–bluish red cutaneous nodules that tended to enlarge into dome-shaped tumors. Kaposi observed similar neoplasms of the mucosa, especially of the larynx, trachea, stomach, liver, and colon. Kaposi's original 1872 description of 5 patients is more similar to the KS seen in AIDS (KS-AIDS) than the KS expected in elderly men of Italian, Jewish, or Mediterranean linkage, in whom the disease behavior is benign. Kaposi's original 5 patients died

within 2-3 years. Kaposi later updated his data, noting that all of his 16 patients were men with a prognosis that remained unfavorable.
For most of the first 3 quarters of the 20th century, KS was viewed as an indolent slowly growing cancer, and patients were expected to die with, rather than of, KS. The aggressive course originally noted by Kaposi has become part of the devastation of AIDS, especially among men who are homosexual.
American AIDS was identified relatively recently (1981) in 3 reports of KS as an original defining element of AIDS (plus an important editorial and a Centers for Disease Control and Prevention *Morbidity and Mortality Weekly Report* bulletin). Two of the reports were from New York City, and 1 was from San Francisco. For some time, KS was seen in 30-40% of patients with AIDS, often as the presenting sign. The incidence of KS has fallen markedly in recent times, although its prevalence has not. The challenge remained to explain the reason patients who are homosexual and have AIDS exhibited KS much more commonly than did patients with AIDS unassociated with homosexuality, with the exception of small foci of homosexuals in isolated midwestern communities.
The breakthrough came in 1994, when the KS-associated herpes virus (human herpesvirus type 8 [HHV-8]) was identified using representational difference analysis. HHV-8 has been linked closely with all 4 types of KS, i.e. classic (traditional), endemic (African), epidemic (AIDS related), and iatrogenic (related to immunosuppression). Since then, much research has shown that HHV-8 appears to be necessary to, but not sufficient for, the development of KS.
Nevertheless, 2 critical questions remain. Is KS a hyperplasia or a neoplasm? Is it always multicentric or can it be metastatic as well? The authors favor the latter interpretation of both points.
**Pathophysiology.**HIV transactivating (tat) gene, cytokine, and HHV-8 stories in KS are fascinating. Each begins with a classic study. In 1988, the human immunodeficiency virus type 1 (HIV-1) tat gene was introduced into transgenic mice, inducing nodules that resembled KS in 33 of 37 males but in none of 15 females. Therefore, it appeared that HIV could play a direct role in causing KS.
The second saga was a result of efforts to grow KS cells in culture, requiring a long-term growth factor. Conditioned medium from T cells infected with human T-cell leukemia virus type II (rather than HIV-1 or human T-cell leukemia virus type I) best supported the growth and long-term culture of KS cells derived from KS-AIDS lesions. In 1992, this growth factor proved to be a cytokine previously termed oncostatin M, since it had been identified earlier for its inhibitory effects on a variety of cancer cells. Another cytokine scatter factor was found in large quantities in this medium, inducing endothelial cells to demonstrate a KS tumor cell-like phenotype. The importance of oncostatin M, scatter factor, and the tat protein has been shown in the pathogenesis of KS.
Other cytokines, including interleukin 1 (IL-1), tumor necrosis factor, interleukin 6 (IL-6), and basic fibroblastic growth factor (bFGF), may work synergistically with the HIV tat gene product. Scatter factor may be involved both in initiation and in maintenance of KS. Scatter factor stimulates endothelial cells to migrate nearby

and become factor XIIIa–positive *c-Met*-expressing spindle-shaped KS cells. The cells further expand neovascularization by producing cytokines and promoting autocrine-mediated and paracrine-mediated growth of KS cells. The scatter factor receptor, *c-Met* proto-oncogene, is expressed by KS cells; the oncogene *int-2* of the fibroblast growth factor family also may be evident.

Herpes-type viruses have been linked with KS for more than 3 decades. A landmark study showed short DNA sequences of a unique human herpesvirus in KS tissues via a new molecular biological technique termed representational difference analysis. They resembled herpesvirus saimiri but proved to be a new type of human herpesvirus now termed HHV-8. This virus appears to interact with the HIV tat protein, excess levels of basic fibroblast growth factor, scatter factor, and IL-6. For example, HHV-8–encoded IL-6 has been found to induce endogenous human IL-6 secretion. An HHV-8 oncogene, Kaposin (*ORF K12*), has been characterized; however, additional factors remain to be found. For example, a 53% prevalence of HHV-8 subtype E in Brazilian Indians does not appear to be linked with the development of KS in this population.

Classic KS is seen in Italy with hot spots being in the Po River Valley, Sardinia, and southern Italy. It has been suggested that volcanic soil or birthplace/residency in areas abundant with bloodsucking insects may be a risk factor (Ascoli, 2003). A survey evaluated the correlation between HHV-8 infection and classic KS incidence in northern Sardinia (Santarelli, 2001). It revealed that seroprevalence was 35%, within a range of 15.3-46.3% in the five areas. Age was as an important risk factor. Subjects aged older than 50 years had a higher seroprevalence to HHV-8 as compared with younger individuals. A strong direct correlation between HHV-8 prevalence and classic KS incidence was also observed.

KS-associated herpesvirus (KSHV), or human herpesvirus 8 (HHV-8), is the most frequent cause of malignancy in patients with AIDS (Moore and Chang, 2003). KSHV and related herpesviruses have pirated cellular cDNAs from the host genome. Many of the viral regulatory homologs encode proteins that directly inhibit host adaptive and innate immunity. Other viral proteins may target retinoblastoma protein and p53 control of tumor suppressor pathways, which play key effector roles in intracellular immune responses. The immune evasion strategies used by KSHV in targeting tumor suppressor pathways activated during immune system signaling, may lead to inadvertent cell proliferation and tumorigenesis in susceptible hosts.

**Frequency.**Four groups are predisposed to KS including (1) older men of Mediterranean and Jewish lineage; (2) Africans from areas including Uganda, the Congo Republic, Congo (Brazzaville), and Zambia; (3) persons who are iatrogenically immunosuppressed; and (4) men who are homosexual. KS traditionally is an uncommon disease in middle-aged and elderly European men of Mediterranean or Jewish lineage. A similar focus of KS exists in the same age and sex groups in Africa. If a crudely calculated incidence of 28 cases of KS per 100,000 in the Arabian population is correct, KS may be more common among Arabians than among Mediterranean people. A previously unrecognized genetic

predisposition for KS among Arabians has been suggested. The incidence of KS among renal transplant recipients may be as high as 3.5% or higher in regions endemic for KS, which is significantly higher than the 0.4% incidence renal transplant recipients in the United States and Western Europe.

Endemic African KS has accounted for 10% of cancers and has been seen in a male-to-female ratio of 15:1. The Kampala Cancer Registry, one of the continent's first and foremost, has shown a significant alteration in the incidence of KS in the era of AIDS. In Uganda, KS has caused almost one half (48.9%) of cancer cases in men and 17.9% in women.

Classic KS in Greece seems to have an older age of onset; lower male-to-female ratio; endemic clustering; and disseminated skin disease at diagnosis, often accompanied by lymphedema and not unusual visceral or lymph node involvement.

**Mortality/Morbidity.**Patients with traditional KS tend to die with KS rather than of KS. Patients with KS-AIDS usually die from associated opportunistic infections or from gastrointestinal KS with hemorrhage. The mean survival rate of patients with KS-AIDS has been approximately 15-24 months, although the introduction into the United States of apparent immune system reconstitution using highly active antiretroviral therapy (HAART) has extended survival substantially. KS also may be fatal as a result of gut perforation, cardiac tamponade, massive pulmonary obstruction or, rarely, brain metastases.

In Kaposi's original description, death usually ensued within 3 years and was linked to fever, diarrhea, and hemoptysis. Inanition may be an important factor, and death may ensue as a result of bulky tumor obstructing the bronchi or larynx.

Patients with AIDS-related KS often have widespread visceral KS, although KS limited to the skin also is common.

Patients with iatrogenic KS tend to have gut bleeding resulting from KS, although termination or reduction of immunosuppression often, but not always, results in regression of KS.

**Causes.**HHV-8 has been linked convincingly with all 4 types of KS, an association that is necessary, but not sufficient, to develop KS; therefore, other factors also are important. At this point, immunosuppression appears to be the most significant cofactor.

**Race.**KS is an uncommon disease of middle-aged and elderly American and European men of Mediterranean or Jewish lineage. This propensity also is seen in individuals with iatrogenically induced KS but not among persons in the KS-AIDS group. KS is rare in American blacks, despite its large foci among blacks in certain regions of Africa.

**Sex.**Classic KS has an overwhelming male predominance, with a male-to-female ratio of approximately 10-15:1. For endemic KS in Central Africa, the male-to-female ratio is near unity in childhood KS cases but often rises in puberty to 15:1. In Corsica and Sardinia (where classic KS is endemic), with the arrival of AIDS, the ratio of male-to-female cases has dropped from 10:1 to 3:1. Children of women who are HIV-1 seropositive without KS have an aggressive form of childhood

HIV-associated KS. A male-to-female ratio of 1.5:1 was observed. A male-to-female ratio of 1.5:1 also was evident among renal transplant recipients in Arabia.

**Age.**Age distribution depends on the type of KS. In the United States and Europe, traditional KS has a peak incidence between 40-70 years, with a wide range of up to 89 years. Young men with KS-AIDS who are homosexual also show a wide age range but tend to be much younger, averaging 20-40 years at age of onset. For endemic KS in Uganda, the incidence in boys and girls was approximately the same in childhood (birth to 14 y), with a small peak in girls younger than 5 years and boys aged 5-9 years. Subsequently, a progressive rise in incidence peaked in women aged 25-29 years and in men aged 35-39 years.

**History.**KS is a neoplasm that often manifests with multiple vascular nodules in the skin and other organs.Although true metastases appear to occur, a multifocal origin is most common.The pattern of KS is variable, with a course ranging from indolent (only skin manifestations) to fulminant (extensive visceral involvement).KS also may arise primarily in the oral mucosa, lymph nodes, and/or viscera without skin involvement.KS initially may be evident in any organ of the body. Chronic lymphedema may precede KS.

Although primary penile KS is uncommon in HIV negative men, one should consider this possibility when treating nonspecific penile lesions. A minimal penile lesion with non-distinctive clinical features may be the exclusive manifestation of KS. In addition, it may appear as a skin-colored nodule suggestive of a primary squamous cell carcinoma. Clearly, in both cases, histologic evaluation is mandated to establish the diagnosis.

**Physical.**KS is described in 3 forms including localized nodular, locally aggressive, and generalized KS. KS typically occurs in these 3 forms and in 6 stages including patch, plaque, nodular, exophytic, infiltrative, and lymphadenopathic.

***Cutaneous KS*** usually begins as discrete red or purple patches that are bilaterally symmetric and initially tend to involve the lower extremities.Patches become elevated, evolving into nodules and plaques. Nodules may be spongy to the touch. KS also occurs as a large infiltrating mass or as multiple cone-shaped friable tumors. These 2 variants, termed locally aggressive KS, may adhere firmly to underlying anatomic structures including bone.Early KS may appear as violaceous patches (patch stage KS), which occasionally resemble large junctional melanocytic nevi or may appear as irregular-shaped patches similar to the nevus flammeus.More commonly, KS is evident as violaceous plaques or nodules on the lower extremities. The nodules tend to enlarge into dome-shaped tumors.Cutaneous KS rarely may be infiltrative or exophytic. To the authors' knowledge, infiltrative KS has not been described outside of Africa. Exophytic KS may erode downward into bone.Lymphadenopathic KS may demonstrate skin lesions. At times, a Köbner phenomenon appears evident, with nodules at sites of trauma.

A few unusual varieties of KS also exist. ***Telangiectatic KS*** is an eruption of pink translucent nodules with prominent telangiectasia.***Ecchymotic KS*** appears as

periorbital ecchymoses. Histologically, there is a large amount of extravasated red blood cells, no evidence of amyloidosis, and a dermis containing foci of proliferating moderately atypical spindle cells, vascular slits, erythrophagocytosis, and other features of KS.***Keloidal KS*** is evident as somewhat brown-to-violaceous keloidal nodules. Histologically, these are KS nodules with a keloidal component.***Cavernous KS*** is a rare type of locally aggressive KS characterized by cutaneous tumors that histologically resemble cavernous hemangiomas; however, the endothelial cells and their nuclei are large and prominent, bulging into the cavity.***Lymphangioma-like*** KS is a rare variant in which dilated vascular spaces produce a bullous-appearing eruption, typically on the lower legs. The lesions are easily compressible and appear clinically to be fluid-filled. The vascular channels are lined by banal-appearing endothelial cells permeating the dermis in the absence of spindle cell proliferation.

**Lab Studies.**Serum glucose levels may reflect an increased incidence of diabetes mellitus in patients with classic KS. Ketoacidosis is unusual in these patients.Immunohistochemical detection of human herpes virus-8 latent nuclear antigen-1 has been claimed as useful in the diagnosis of KS.Hemogram in non-immunosuppressed patients with KS tends to be within normal limits, but occasionally, monocytosis or eosinophilia has been noted. Eosinophilia is seen especially in African patients and patients who are homosexual, in whom parasitosis may be common.In KS-AIDS, cytopenia of 1 or more cell lines is frequent. Anemia, if present, may result from gastrointestinal bleeding or may be associated with an autoimmune hemolytic anemia or a hematologic malignancy.Assays for HHV-8 have been challenging. At present, no universally accepted method exists.Polymerase chain reaction often is used but may have false-positive results because of its high susceptibility to contamination.Methods based on both lytic and latent-phase viral antigens remain promising.

**Imaging Studies.**Computed tomography (CT) may be valuable, especially abdominal CT scans in patients with AIDS.In AIDS-related KS, early lymphatic and hepatosplenic involvement may be evident.Consider CT-directed fine needle aspiration to provide tissue confirmation, since lymphomas and atypical mycobacterial and other infections may appear similar.Consider endoscopic and conventional radiographic studies; however, these modalities may miss gastrointestinal KS, while selective angiography may demonstrate KS.Radionucleotide scans may be useful in demonstrating visceral KS and associated lymphoma.With lung nodules, the distinction between KS, lymphoma, and/or opportunistic infection may be challenging.

**Other Tests.**Evaluation for KS should include a complete physical examination and a biopsy of suspected lesions including lymph nodes. CT scan used to guide a fine needle for tissue specimens appears promising.The cell of origin in KS remains a subject of dispute, although the following tests may be useful: ultrastructural and immunohistochemical testing favor the endothelial cell.The presence of factor VIII–related antigen, human leukocyte antigen DR (HLA-DR), von Willebrand factor, and the lectin Ulex europaeus I (which all are markers for

endothelial cells) is highly suggestive.Reactivity with 2 monoclonal antibodies (EN4 and PAL E) implies that KS is derived from endothelium of lymphatic origin; however, KS spindle cells express CD34 antigen, a glycoprotein expressed by endothelial cells of small blood vessels (but not those of lymphatic origin).

**Histologic Findings.**KS tends to demonstrate increased spindle cells with vascular slits and vascular structures with a predominance of endothelial cells. Extravasated erythrocytes and hemosiderin-laden macrophages often are evident. Some spindle cells may show nuclear pleomorphism. Early KS may resemble granulation tissue with a diffuse chronic inflammatory infiltrate and capillaries dilated and increased in number. This pattern also is seen in lymph nodes and viscera. Histopathologic classification is based on relative contribution of spindle cells, fibrosis, and nuclear pleomorphism, sometimes divided into 3 histopathologic forms, which include (1) a mixed form with an equal amount of spindle cells, vascular clefts, and capillaries, (2) a mononuclear type with 1 cell type predominating, and (3) an anaplastic form with cellular pleomorphism and numerous mitotic figures.

The electron microscopy and immunohistochemical features of KS may be important. Staining with CD34, factor VIII–related antigen, the lectin Ulex europaeus I, and HLA-DR antigen may be useful to support or confirm the diagnosis of KS. The authors prefer CD34 antigen, which is expressed by KS cells, and find it helpful in distinguishing KS from pseudo-KS (acroangiodermatitis).

**Medical Care.**Since the natural history of KS is variable, assessment of therapy may be difficult. Treatment usually is based on the extent of disease and the patient's immune status. The optimal therapy of KS-AIDS is yet to be determined. The challenge is to treat KS-AIDS effectively without immunocompromising the patient further, or better, with reconstitution of the immune system. Management modalities for KS include nonintervention, surgical removal of skin nodules or severely affected areas (e.g. areas of the extremities, intussuscepted bowel), laser surgery, conventional and megavoltage radiotherapy, chemotherapy, immunotherapy, antiviral drugs, and cessation of immunosuppressive therapy in iatrogenically immunosuppressed patients. Indolent skin tumors in elderly white patients may not require specific therapy early in the course of the disease; however, systemic vinblastine (or other chemotherapy) attacks both cutaneous and visceral lesions.Localized nodular disease may respond well to surgical excision, radiotherapy, and intralesional and outpatient low-dose vinblastine chemotherapy. The latter combination of local and systemic regimens may be preferable. The authors usually inform patients that this is a multicentric disease that has silent gut lesions that also may regress with the systemic approach.

Radiotherapy often produces good therapeutic results with classic nodular KS but tends to be only palliative in patients with KS and AIDS. In localized nodular KS, conventional radiotherapy is highly effective. Electron-beam radiotherapy, which has limited penetration beyond the dermis, may be a good modality for superficial lesions. Deeper or unresponsive KS may be treated using standard non–electron-beam radiation or other options. Initial response to radiotherapy usually is complete or demonstrates marked regression of the nodules. The more extensive

the involvement, the less responsive it tends to be. Radiotherapy may be more effective on new, rather than chronic, lesions and may provide local KS control in patients with KS-AIDS.Radioisotope scanning using technetium-99m may detect occult KS infiltration in the subcutaneous and muscular tissues and draining lymph nodes. This allows improved efficiency of large-field radiotherapy.

Laser therapy: Argon laser photocoagulation therapy also may be beneficial in classic KS lesions.The authors' preference often is the Klein regimen of weekly outpatient intravenous vinblastine titered against white cell count levels to avoid falling below 4000/L. The authors recommend intralesional injections of vinblastine for persistent cutaneous nodules and intraarterial vinblastine in certain settings for locally aggressive KS. Systemic vinblastine (3.5-10 mg IV weekly with, at times, 1 intralesional injection of 0.1 mg) usually is best for both the patient with classic KS and, occasionally, patients with KS-AIDS.

Although the authors prefer low-dose vinblastine, a number of other chemotherapeutic agents may be effective. Drugs with proven efficiency include vincristine, vinblastine, dacarbazine, doxorubicin, and actinomycin D. Alkylating agents (e.g. cyclophosphamide, chlorambucil, bleomycin, doxorubicin, etoposide) also may be of value. Multiagent intravenous chemotherapy, rather than single agent usage, is preferred by some for disseminated aggressive KS. No particular combination regimen has been established yet. The combination of doxorubicin, bleomycin, vinblastine, and dacarbazine may be effective.

Alternating vincristine and vinblastine in patients with KS-AIDS can be both effective and well tolerated, but leukopenia and a propensity to opportunistic infections make aggressive chemotherapy difficult. Patients with KS-AIDS usually succumb either to disseminated KS or to an intervening opportunistic infection within 3 years of diagnosis, regardless of the form of therapy (except with HAART therapy). All of these therapies (except low-dose vinblastine) are significantly immunosuppressive and, perhaps, accelerate the disease. Combining chemotherapy for KS with chemotherapy for HIV is an attractive option. Interferon also may be used in this way. Thus, the combination of zidovudine, interferon, and low-dose intravenous vinblastine may be used for patients with KS-AIDS.

In iatrogenic KS, cessation of immunosuppressive therapy may be the most effective treatment. Patients on immunosuppressive therapy, specifically corticosteroids and cytotoxic drugs, may have partial or complete regression when therapy is discontinued. If possible, immunosuppressive medication doses should be reduced or discontinued before beginning specific therapy for iatrogenic KS.

In some patients, KS-AIDS may resolve clinically with the use of HAART. Antiviral therapy with foscarnet may not only reduce progression of KS in patients, but may lower its occurrence substantially in patients with HIV disease.

**Consultations.**Treating patients with advanced KS often requires a team approach. Medical oncologists often administer systemic chemotherapy. Radiation oncologists tend to favor radiotherapy options. Infectious diseases/HIV specialists may be needed for HIV and opportunistic infections.

**Prevention.**Reducing the HHV-8 infection rate prevents KS development. Suggestions have been made that some antiherpetic agents, particularly foscarnet, may lower the HHV-8 infection rate.Screening transplant recipients for HHV-8 infection may be beneficial. Use of the highly active anti-HIV therapy HAART appears to reduce the risk of developing new KS significantly.
**Complications.**The most common complications include secondary malignancy and secondary infections. In particular, secondary infection occurs with the KS-AIDS group of patients. A relatively common clinical concern is to distinguish KS from opportunistic infection and lymphoma.In patients with classic KS, lymphoma develops in approximately 35%, usually after a number of years.KS may produce clinical problems including edema from impaired lymphatic draining (sometimes resulting in pain), difficulty ambulating, friability of cutaneous nodules, or secondary localized skin infection.
**Prognosis.**Clinical classification of KS may be the best prognosticator, comparing localized nodular disease, locally aggressive disease, and generalized KS.Cutaneous skin testing for anergy may correlate with clinical disease type and prognosis.Prognosis appears to correlate with the CD4 count. Localized nodular KS has the best prognosis, with few deaths directly attributable to KS.Locally aggressive KS has an intermediate prognosis. The authors do not disagree with an old African estimate of a 3-year survival rate of 64%. Generalized KS, the form seen most commonly in patients with KS-AIDS, has a 3-year survival rate closer to 0% without therapy.

## 16.5. Pigmented Purpuric Dermatitis

**Synonyms and related keywords:** capillaritis, benign pigmented purpura, pigmented purpuric eruptions, Schamberg disease, progressive pigmentary dermatosis, itching purpura of Loewenthal, eczematidlike purpura of Doucas and Kapetanakis, pigmented purpuric lichenoid dermatosis of Gougerot and Blum, lichen aureus, purpura annularis telangiectoides, purpura annularis telangiectodes, Majocchi diseases.

**Background.**The pigmented purpuric dermatoses are a group of chronic diseases of mostly unknown etiology that have a very distinctive clinical appearance. They are characterized by extravasation of erythrocytes in the skin with marked hemosiderin deposition.
A number of clinical patterns of pigmented purpuric dermatoses or capillaritis are recognized that may represent different presentations of the same disorder; however, this generally does not influence the treatment or the prognosis. They all show a similar histologic appearance. The term pigmented purpuric dermatoses includes Schamberg disease (i.e. progressive pigmentary dermatosis), purpura annularis telangiectodes (Majocchi disease), lichen aureus, itching purpura, eczematid-like purpura of Doucas and Kapetanakis, and the pigmented purpuric

lichenoid dermatosis of Gougerot and Blum. Many consider itching purpura and eczematid-like purpura to be variants of Schamberg disease.

**Pathophysiology.**The etiology is unknown. Venous hypertension, exercise, and gravitational dependency are important cofactors that appear to influence disease presentation. Histologically, a perivascular T-cell lymphocytic infiltrate is centered on the superficial small blood vessels of the skin, which show signs of endothelial cell swelling and narrowing of the lumen. Extravasation of red blood cells with marked hemosiderin deposition in macrophages is also found, and a rare granulomatous variant of chronic pigmented dermatosis has been reported.

**Frequency.**During a 10-month period, the authors' United Kingdom hospital-based dermatology practice, which serves a population of 300,000 persons, identified only 10 such cases. Five cases were diagnosed as having lichen aureus, and the remainder had more extensive capillaritis. In the US: Pigmented purpuric dermatoses are uncommon.

**Mortality/Morbidity.**Typically, the condition is asymptomatic, but pruritus may sometimes be a prominent feature in some cases, especially in patients with itching purpura.

**Age.**Schamberg disease may occur at any age. Itching purpura and the dermatosis of Gougerot and Blum mainly affect middle-aged men. Lichen aureus and Majocchi disease are predominantly diseases of children or young adults.

**History.**Patients complain about the appearance of their skin. In Schamberg disease, irregular plaques and patches of orange-brown pigmentation develop on the lower limbs. The lesions are chronic and persist for years. With time, many of the lesions tend to extend, but some may spontaneously clear.In itching purpura, the lesions are much more extensive, and patients typically complain of severe pruritus.

**Physical.**The hallmark of a pigmented purpuric dermatosis is its characteristic orange-brown, speckled, cayenne pepper–like discoloration. The lower limbs are affected in Schamberg disease, whereas itching purpura is characterized by more generalized skin involvement.In lichen aureus, the eruption is usually a solitary lesion or a localized group of lesions that may affect any part of the body; however, the leg is the most commonly affected area. Linear or quadrantic forms of lichen aureus have been reported.Majocchi disease is characterized by small annular plaques of purpura that contain prominent telangiectasia.Pigmented purpura with lichenoid-type skin change is yet another clinical variant, which Gougerot and Blum first reported.

**Lab Studies.**A complete blood cell count is necessary to exclude thrombocytopenia, and coagulation screening helps to exclude other possible causes of purpura.

**Imaging Studies.**Dermoscopy has been reported to be a useful tool for assisting the clinical diagnosis of pigmented purpuric dermatoses.

**Other Tests.**Capillary fragility may be assessed by the Hess test.

**Procedures.**A skin biopsy helps to confirm the diagnosis of a pigmented purpuric eruption and aids in excluding cutaneous T-cell lymphoma, which in its early

stages may closely mimic a pigmented purpuric dermatitis both clinically and histologically.

**Histologic Findings.**Histologically, a perivascular infiltrate of lymphocytes and macrophages is centered on the superficial small blood vessels of the skin. Signs of endothelial cell swelling and narrowing of lumina may be seen. The infiltrate is composed of predominantly $CD4^+$ lymphocytes along with occasional $CD1a^+$ dendritic cells. Plasma cells and neutrophils are occasionally present; the latter is not uncommon in lesions of itching purpura. Extravasation of red blood cells with marked hemosiderin deposition in macrophages is typically seen. However, the degree of hemosiderin deposition may be variable, and it can be minimal in early lesions of itching purpura.

Histochemical staining with Perls stain and Fontana-Masson stain, to demonstrate iron (hemosiderin) and exclude melanin pigment respectively, may be helpful. Hemosiderin deposition in the dermis is more superficial in pigmented purpuric dermatitis than that seen in stasis dermatitis, which is a useful differentiating feature. Mild epidermal spongiosis and exocytosis of lymphocytes may be seen in all variants except lichen aureus, which, in general, tends to show a band-like infiltrate separated from the epidermis by a thin rim of uninvolved collagen.

**Medical Care.**No medical intervention is of proven benefit for the treatment of the pigmented purpuric dermatoses. Pruritus may be alleviated by the use of topical corticosteroids and antihistamines.Associated venous stasis should be treated by compression hosiery. Prolonged leg dependency should be avoided.

**Prognosis.**Many lesions persist or extend with time. Most eventually resolve spontaneously.

# XVII. WORK-RELATED SKIN DISEASES

## 17.1. Characteristics of Work-Related Skin Diseases

Work-related skin diseases show a wide range of clinical features and originate from damaging factors at the work place. In many occupations, the skin is exposed to damaging factors like chemicals, biological material and mechanical and physical forces. This exposure can cause damage to the skin. The sensitivity of the skin to damage and its ability to recover varies from one individual to another. Work-related skin diseases develop if the balance between the resistance of the skin and the force of damaging factors is disturbed. The severity and course of the skin disease is determined by the quality of the skin, the characteristics of the damaging factors and the medical treatment. The damage can range from a brief, burning sensation to a disabling chronic eczema. Early recognition of the relation between the disease and the occupation combined with adequate management that focus more on the workplace than on the skin, can prevent chronicity with a poor prognosis.

**Work-related skin disease is defined as a disease to with occupational exposure is a causal or contributory factor.** This definition of the American Medical Association in 1939 is still valid today.

### Skin Damaging Mechanism

The dynamic interaction between the chemical, physical and mechanical characteristics of the damaging factor(s) and the biological make-up of the skin determine the degree of the molecular, histological and anatomical damages of the skin, expressed in a range of visible and subjective symptoms.

The most common work-related skin diseases develop almost unnoticed as an accumulation of repeated minor damages caused by a variety of different factors to which the skin is exposed simultaneously or one after the other. In the initial stage, the damage is invisible to the human eye. This damage triggers the release of cytokines and these initiate and orchestrate an inflammatory reaction to restore the damage. However, the ongoing damage can exceed the skin's ability to repair itself, and visible skin diseases then appear: erythema, scaling, swelling, vesicles, rhagades and papules.

The skin damage can also be acutely overwhelming, with immediate severe damage to inter (cellular) structures, e.g. acute chemical burns with erythema, swelling, bullae and necrosis.

Damage caused by other factors may be focused on certain components of the skin, e.g. melanocytes by hydroquinone, resulting in depigmentation, or DNA by chronic exposure to UV-light inducing skin malignancies. Skin damage can also develop after triggering of the immune system, by layer of the epidermis the Langerhans cell plays a central role in the orchestration of this immune response. If

sensitization is induced, renewed exposure to the allergen initiates a defense response amplified by T-cells and antibodies, creating a severe skin disease in a short time (minutes to days).
Work-related skin diseases are distinguished from other skin diseases by characteristics revealed by physical examination combined with the analysis of occupation, working conditions and the course of the skin disease.

**Physical examination.**The clinical features and localization provide important arguments for or against a work relation. Pre-existing skin diseases are important modifying factors for the development of a work related skin disease.
**Clinical features.** The majority of work-related skin diseases occur as dermatitis or eczema. The following features may also be observed: erythema, vesicles, bullae, fissures, rhagades, edema, papules, urticaria, erosions, pustules, necrosis, folliculitis, tumors, prurigo, hyperpigmentation and depigmentation.
**Localization.**Work related skin diseases generally appear on the exposed areas of skin, which are mainly the uncovered skin parts like hands, wrists, forearms, the proximal part of the upper arm, neck, face, eyelids and ears.
**Pre-existing skin condition.Atopy:** Atopic dermatitis in flexures of elbow and knee, on the lips, hands, neck and face. **Dry skin:**Dry skin with fine scaling.**Psoriasis:**The typical erythemato-squamous lesion on covered skin, but also psoriasis stigmata on the head, in the ears, on the nails and the elbows or knees.
**Causes of work - related diseases and risk occupations**
Skin may be damaged by biological or synthetic chemical compounds, by physical influences and mechanical forces. The severity of the disease is determined by the characteristics of the damaging factors, combined with the type of exposure, such as:
• Concentration or strength
• Duration of exposure
• Frequency of exposure
• Temperature of the damaging factor
• Temperature of the skin
• Localization of exposure

The following factors can be viewed upon as possible causes of work-related skin diseases:**Irritants**

| | |
|---|---|
| **Acids and alkalis** | **Adhesives** |
| **Air flow** | **Animals** |
| **Atmospheric humidity** | **Cold** |
| **Cosmetics** | **Detergents** |
| **Force of gravity** | **Heat** |
| **Meat and fish** | **Mechanical forces such as pressure and friction** |
| **Metal working fluids such as cooling fluids and cutting** | |
| **Mineral fibers** | **Oxidizing and reducing agents** |
| **Paints** | **Pesticides** |
| **Plants, vegetables and fruits** | **Plastic materials, preservatives** |
| **Rubber** | **Solvents** |
| **UV-light** | **Water** |

## Allergens

Biological or synthetic chemical compounds may induce type I and type IV allergies of the skin. Some allergens occur in many products, exposing individuals at home and work, e.g. rubber and nickel. Other allergens are present in products with a specific use, e.g. ingredients of permanent wave fluids or adhesives. Table 17.1 shows product groups containing type IV allergens

### Table 17.1 Product Groups Containing Type IV Allergens

| Product Group | Allergen |
|---|---|
| Adhesives | Epoxy resin<br>Epoxy hardeners<br>Phenol formaldehyde resins<br>Acrylates<br>Rosin |
| Cosmetics | Fragrances<br>Peru balsam<br>Rosin<br>Cocamidopropil betaine<br>Preservatives |
| Metals | Nickel<br>Cobalt<br>Dichromate |
| Metal working fluids | Preservatives<br>emulsifiers<br>amines |
| Plants | Promin (primula)<br>Tulipalin-A (alstroemeria-tulip)<br>Sesquiterpene lactones (chrysanthemums) |
| Plastics | Epoxy resin<br>Epoxy hardeners<br>Di-isocyanates<br>Acrylates |
| Preservatives | Methyldibromoglutaronitrile<br>Methylchloroisothiazolinone/metylisothiazolinon |

| | |
|---|---|
| | Quaternium-15 |
| Professional hair cosmetics | Glycerilthioglycolate<br>ammonium persulphate<br>4-phenylene diamine<br>2,5-diaminotoluenesulphate |
| Rubber | Thiuram compounds<br>Mercapto cmpounds<br>Black rubber compounds<br>Latex |

The following occupations are considered to be at risk of work-related skin diseases:

## Table17.2 Riskoccupations

| **Industry/Sector** | **Occupation** |
|---|---|
| Agricultural | Frame, flower-, vegetable-and bulb grower, forestry workers |
| Animal healthcare | Vets and veterinary assistants |
| Automobiles | Mechanic, sprayer |
| Bakeries | Baker and confectioner |
| Beauty care | Hairdressers, beauticians, nail stylists |
| Catering and food processing | Cook, bartender, cleaner |
| Chemical industry | Production and laboratory workers |
| Cleaners | Cleaning workers |
| Construction | Bricklayer, joint, plaster, carpenter, plumber, painter, floor layer, roofer |
| Electroplating industry | Production workers |
| Flower shops, garden centers | Florist, gardener |
| Food industry | Vegetable-, fish-, meat- and fruit-processors, bakers and confectioners |
| Healthcare | Doctor, nurse, paramedic personnel, dental technicians, dentists, physiotherapists, laboratory workers, maternity, hospital and geriatric nurses |
| Homework | Housewife/husband, housekeeper |
| Laboratories | Chemist analyst, laboratory worker |
| Metal industry | Metalworker, construction worker |
| Paint industry | Production and laboratory workers |
| Pharmaceutical industry | Production and laboratory workers |
| Photography | Laboratory assistant |
| Plastics industry | Production workers, laboratory assistant |
| Printing | Printers, lithographers |
| Public service | Cable layers |
| Retail trade | Personnel in the meat, fish, vegetable, sandwich and last food shops |

| | |
|---|---|
| Rubber industry | Production and laboratory workers |
| Service sector | Cleaners, domestic workers, laundry workers |
| Slaughterhouse | Production workers |
| Swimming baths | Cleaners |
| Textile industry | Production workers |

Since the product composition, production methods and working conditions are changing the list of risk occupation will never be complete. In the future new risk occupations will appear and others disappear.

**Diagnosis**

The diagnosis is the outcome of a process of observing, collecting and interpreting facts. These facts are derived from clinical inspection, history, patch testing, microscopy, bacterial culture, histopathology and – last but not least – workplace inspection. Sometimes a definite diagnosis can be made just with a glance but additional investigations are often necessary.

Work-related skin diseases show a wide range of clinical features. The majority of diseases are caused by irritant and/or allergic factors, and are visible as dermatitis or eczema. The damaging factors reach the skin directly or by air (airborne). Sunlight may play a role in the induction of the disease. The following diagnoses of work-related skin diseases can be made:

**Table 17.3 Diagnoses**

| **Diagnoses** | |
|---|---|
| **Direct contact** | **Airborne:** |
| | Airborne irritant contact dermatitis |
| Acute irritant contact dermatitis | Airborne allergic contact dermatitis |
| Sub-acute irritant contact dermatitis | **Sunlight** |
| Chronic irritant contact dermatitis | Phototoxic contact dermatitis |
| Allergic contact dermatitis | Photoallergic contact dermatitis |
| Atopic dermatitis | **Others:** |
| Mechanical contact dermatitis | Acne |
| Hyperkeratotis dermatitis | Rosacea |
| Asteatotic eczema | Psoriasis vulgaris |
| Chronic exogenous dermatitis | Leukoderma |
| Immediate contact reactions | Hyperpigmentation |
| Mineral fiber contacts dermatitis | Infections and parasites |
| | Skin malignancies |
| | Chronic venous insufficiency |

**Table 17.4 DiagnosisNavigator**

| **Duration** | **Clinical feature** | **Subjective symptoms** | **Diagnosis** |
|---|---|---|---|
| Acute | Erythema | pain, burning | acute contact dermatitis |
| Sub-acute | Erythema | pain, burning, itching | sub-acute contact dermatitis<br>phototoxic contact dermatitis<br>airborne irritant contact dermatitis |

| | | | |
|---|---|---|---|
| | | | infection |
| Sub-acute | Erythema, bullae | pain, burning | phototoxic contact dermatitis<br>(sub)-acute contact dermatitis |
| Sub-acute | Erythema, vesicles, bullae | itching, burning | immediate contact reaction<br>phototoxic contact dermatitis |
| Sub-acute | Dermatitis/eczema | Itching | allergic contact dermatitis<br>photoallergic contact dermatitis<br>airborne allergic contact dermatitis<br>airborne irritant contact dermatitis |
| Sub-acute → chronic | Prurigo papules | Itching | mineral fiber contact dermatitis<br>parasitic prurigo |
| Chronic | Dermatitis/eczema | Itching | allergic contact dermatitis<br>chronic irritant contact dermatitis<br>atopic dermatitis<br>photoallergic contact dermatitis<br>airborne irritant contact dermatitis<br>airborne allergic contact dermatitis<br>asteatotic eczema<br>chronic exogenous eczema |
| Chronic | Hyperkeratosis, fissures, rhagades | Pain | psoriasis<br>mechanical contact dermatitis<br>allergic contact dermatitis<br>chronic irritant contact dermatitis |

**The diagnosis navigator is based on:**
**Duration**acute = seconds to hours**;** sub-acute = hours to days
chronic = weeks to minutes
**Clinical features:** erythema, bullae,vesicles urticaria,dermatitis/eczema,prurigo, papules, fissures,rhagades, hyperkeratosis
**Subjective symptoms:** pain,burning, itching

## Clinical Presentationof Work-Related Skin Diseases

### Acute irritant contact dermatitis

***Clinical features:*** burning and pain at exposure site, followed by symptoms such as erythema, bullae, edema, erosions, necrosis and ulcers. The symptoms appear only on the exposed skin.
***Localization:*** mostly on the hands, arms, legs and face
***Pathogenesis:*** damage to intra- and intercellular components of the skin resulting in visible morphological change. Clear dose-effect relationship. The damage may deteriorate under the occlusive effect of clothing, gloves and footwear.
***Agents: e. g.*** chemical and physical agents such as strong alkalis and acids, plastic monomers (acrylates), amines, phenolic compounds, ultraviolet light and heat.
***Course:*** the dermatitis develops within seconds to hours following exposure. Erythema, swelling and bullae disappear in one to two weeks, usually without scarring. If necrosis develops recovery often takes many weeks, with scarring. Excision of the necrosis is sometimes necessary.

**Subacute irritant contact dermatitis**
***Clinical features:*** mostly erythema, bullae and edema. Necrosis is rare.
***Localization:*** hands, arms, legs and face
***Pathogenesis:*** comparable with acute irritant contact dermatitis. However, symptoms appear later, after a few hours to days
***Agents: e.g.*** di-actyl monomers, phenolic compounds, benzalkonium chloride
***Course***: cured within a few weeks. Scarring may develop with necrosis
***Remark***: the clinical features are sometimes difficult to distinguish from (acute) allergic contact dermatitis

**Chronic irritant contact dermatitis**
Synonym: orthogenic eczema or cumulative irritant contact dermatitis
***Clinical features:*** ranging from slight erythema with scaling to eczematous lesions with pronounced rhagades.
***Localization:*** hands, wrists, arms, feet, sometimes the face. The fingertips, inter-digital webspace and the dorsal side of the fingers are often affected.
***Pathogenesis:*** caused by the repetition of the same damaging factor or the cumulative effect of a variety of minor damaging factors. In many "wet work" occupations the clinically normal skin is damaged at a sub-clinical level by exposure to water and detergents. A slight erythema with fine scaling is often the first visible lesion. A sudden change in occupational exposure or in clinic conditions may push the damage"over the edge" to a frank dermatitis or eczema.
***Agents: e.g.***water***,*** soap, detergents, organic solvents, alkalis and acids, fruit and vegetable juices; dry, abrasive materials; metalworking fluids, cement, disinfectants, skin care products, cosmetics; climate: low absolute humidity, dry air flow.
***Course:*** the lesions develop gradually and can suddenly deteriorate. Time off work alone usually gives no rapid cure and the dermatitis tends to a chronic course

***Remark: differentiation of an allergic contact dermatitis is sometimes difficult, even histology not providing a conclusive answer. Negative allergy tests support a diagnosis of chronic irritant contact dermatitis.***

**Allergic contact dermatitis**
Synonym: contact eczema
***Clinical features:***Type IV allergens induce skin diseases with a range of lesions. This varies from a few vesicles on one finger, to sharply demarcated patches of erythema on the back of the hand and up to an extensive and severe eczema with severe edema on the hands, arms and face, itching is often a characteristic symptom.
***Localization:*** the hands, wrists, forearms, eyelids, face, neck and feet.
***Pathogenesis:*** Type IV allergens are chemical compounds of natural or synthetic origin. The onset of induction of sensitization varies from months to years, rarely a

few weeks. Exposure to allergen causes skin lesions at the site of contact after 24 to 72 hours. The allergic reaction can be overwhelming so that skin lesions appear outside the place of contact.
***Agents:*** many thousands of compounds may cause a type IV allergy
***Course:*** Exacerbations and remissions are the characteristic course, changing to a more chronic course after a few months. Exacerbations and remissions then gradually disappear.
***Remark:*** with patch testing, false positive and negative reactions can occur. Positive reactions have to be assessed for relevance, because positive test reactions often have no direct causal relationship with the skin disease.

**Atopic dermatitis**
***Clinical features:*** atopic dermatitis is a highly variable skin disease and often influenced by exogenous factors. In most cases atopic hand eczema is more or less symmetrically localized on the back of the hands and fingers and often the wrists. Patches with erythema, edema, lichenification and dryness, sometimes with painful; rhagades on knuckles and wrists, may dominate the appearance.
***Localization:*** work-related causes of atopic dermatitis affect hands, wrists, forearms, neck, face and feet.
***Pathogenesis:*** develops on the basis of an atopic skin constitution, due to reduced quality of the skin barrier and disturbed recovery capacity. Exogenous factors often make a contribution to exacerbations and a chronic course. Water in particular, usually together with soap and detergents, exacerbates a pre-existing atopic dermatitis or induces new lesions. Atopic dermatitis is frequently colonized by Staphylococcus aureus. By way of a super-antigen allergic reaction Staphylococcus aureus may exacerbate the dermatitis
***Course:*** chronic, often maintained by damaging factors
***Remark:*** evaluate the atopic skin constitution with history and physical examination.

**Mechanical contact dermatitis**
***Clinical features:*** erythema with dry adherent scaling. Tendency to rhagades.
***Localization:*** fingertips and/or palms
***Pathogenesis:*** friction, pressure and shearing forces. Handling dry and rough materials may induce a circumscribed dermatitis.
***Agents: e.g.***handling of paper, cardboard, other dry and slightly abrasive material
***Course:*** chronic

**Hyperkeratotic dermatitis**
***Clinical features:*** symmetrically localized hyperkeratotic and well-demarcated lesions. Tendency to fissures and rhagades, no nail dermatitis.
***Localization:***center of the palm, sometimes tip of thumb and little finger
***Pathogenesis:*** unknown. No clear relationship with psoriasis or atopy. Mechanical forces are sometimes involved.

***Course:*** chronic
***Remark:*** differentiate from psoriasis vulgaris.

**Asteatotic eczema**
Synonym: eczéma craquelé
***Clinical features:*** chapping skin with cracks on a red background; borders are irregular, itching is a dominant feature.
***Localization:*** dorsal site of the hands, wrists, upper arm and outside the thighs.
***Pathogenesis:*** asteatotic eczema is a characteristic variant of chronic irritant contact dermatitis.
***Agents: e.g.***excessive exposure to water and soap (washing hands, showering), frequently triggered by climatic changes, particularly when changing to windy bad weather conditions.

**Chronic exogenous eczema**
Synonym: post-occupational eczema or post traumatic eczema.
***Clinical features*:** various from eczematous to psoriasiform.
***Pathogenesis*:** disturbed regeneration capacity of the skin, leading to a chronic, self-perpetuating dermatitis. Often starts as an irritant or allergic contact dermatitis with remissions and exacerbations related to exposure. Gradually becomes chronic, no longer influenced by exposure. Avoiding of exposure is of no benefit.
***Course*:** chronic, no clear periods with exacerbations and remissions.
**Remark: notoriously resistant to medical treatment**

**Immediate contact reactions**
***Clinical features:***symptoms vary from itching, burning and stinging to erythema and urticaria, sometimes with vesicles. Erythema and vesicles may persist and, if exposure continues, eczema appears. Sometimes, symptoms occur outside the direct contact site, combined with rhinitis, conjunctivitis, asthma and even anaphylactic shock.
***Localization:*** sides of fingers, wrists, forearms and face.
***Pathogenesis:***
**1. Immunological immediate contact reactions:** the allergen binds to the IgE on the mast cell membrane resulting in the release of vasoactive mediators, e.g. histamine.
**2. Non-immunological contact reactions:** a direct effect on the blood vessels or the release of vasoactive substances by non-immunological mechanism.
***Agents:***
**1. Immunological direct reactions:** e.g.: meat, fish, fruit and vegetables, natural rubber latex, penicillin, saliva of mammals, wool, gut of pig and sheep.
**2. Non-immunological direct reactions,** e.g.: caterpillars, jellyfish, Peru balsam, camphor, stinging nettles, seaweed, thyme, cayenne pepper, celery, cinnamon compounds

***Course:*** symptoms and lesions appear seconds to hours after contact. Spontaneous recovery in hours to a day. Repeated exposure can cause a chronic dermatitis with an eczematous appearance.
***Remark: prick or scratch tests are indicated if (immunological) immediate contact reactions are suspected. Specific RAST is sometimes available. Generalized urticaria is normally not caused by damaging factors at the workplace.***

**Mineral fiber contact dermatitis**
Synonym: glass fiber or rockwood dermatitis
***Clinical features:*** itching is dominant. Small erythematous papules, sometimes with petechiae, erosions, urticaria and scratches.
***Localization:*** uncovered skin by direct exposure. Covered skin by contamination and penetration of clothing.
***Pathogenesis:*** mechanical irritation.
***Agents:*** glass and rockwood fibers.
Course: symptoms often disappear spontaneously after a few weeks by hardening, even if exposure continues. Work interruption cures the condition after a few weeks, but it can quickly relapse.
***Remarks: mineral fiber dermatitis is usually airborne. Family members may also develop symptoms caused by contamination of clothing in the washing machine.***

**Airborne irritant contact dermatitis**
***Clinical feature:*** Itching and burning sensations on the exposed uncovered skin; sometimes also on covered skin. Erythema, scaling, sometimes eczematous with fissures.
***Localization:*** forehead, cheeks, eyelids, ears, jaws, nostrils, lips, neck, uncovered parts of the arms.
***Pathogenesis:*** the agents come into contact with the skin by the air, as gas, vapour, droplet, spray or dust. Sunlight does not play a role. Pathogenesis is comparable with chronic irritant contact dermatitis.
***Agents: e. g.***alkalis and acids, organic solvents, cleaning agents, plastic agents, plastic monomers, calcium oxalate and silicon oxide, tropical wood sawdust, plant particles, vapour of food components, cement powder, phenolic compounds, fertilizer.
***Course:*** comparable with sub-acute and chronic irritant contact dermatitis.

**Airborne allergic contact dermatitis**
***Clinical feature:*** Itching, erythema, edema, papules, vesicles and scaling. Usually a red, scaling or eczematous picture.
***Localization:*** forehead, cheeks, eyelids, ears, jaws, nostrils, lips, neck, uncovered parts of the arms.
***Pathogenesis:*** Type IV allergy.

***Agents: e. g.*** plants (Compositae family [chrysanthemums]), plastic monomers, pesticides,animal feed ingredients,tropical wood sawdust, chromium salts (cement dust)
***Course:*** comparable with allergic contact dermatitis

**Phototoxic contact dermatitis**
***Clinical features:*** the symptoms mimic sunburn with burning pain, erythema, edema, sometimes vesicles and bullae. Onycholysis and hyperpigmantation may develop at a later stage. The dermatitis is characterized by sharply demarcated erythema, often with blisters, leaving hyperpigmentation.
***Localization:*** sunlight-exposed skin parts, face, neck, chest, back of the hands and arms. Lesions are more pronounced on ears, nose and cheeks. Less on sun-shielded parts such as eyelids, upper lips, neck under the chin. Hypo– and hyperpigmentation may appear.
***Pathogenesis:*** some chemical compounds are activated by UV or sunlight. This activation includes photochemical reactions in the skin which causes cell damage or even cell death. There is a clear relationship between dose and effect. Everyone is at risk. The causative agent enters the skin directly or by the blood flow.
***Agents: e.g.*** plants, such as parsley, bear's breech, dill, celery, rue (Ruta graveolens), skimmia, medication: tetracyclines, furosemide, griseofulvin, psoralentar products.
***Course:*** sub-acute: symptoms appear within a few hours to days. The lesions disappear in days to weeks after avoiding contact

**Photoallergic contact dermatitis**
***Clinical features:*** erythema, edema, papules, vesicles and eczema.
***Localization:*** sunlight-exposed skin parts, like the face, neck, chest, back of the hands and arms. Lesions are more pronounced on ears, nose and cheeks and less on sun-shielded parts such as eyelids, upper lips and neck under the chin. Hypo– and hyperpigmentation may appear.
***Pathogenesis:*** some chemical compounds induce a type IV allergy,under influence of UV or sunlight. This allergic reaction is comparable with allergic contact dermatitis. The agent enters the skin directly or by the blood flow.
***Agents: e.g.*** plants: Composite family (chrysanthemum, marigold, yarrow);cosmetic ingredients: musk ambrette, cinnamic aldehyde; UV blockers (sunscreens);medication: promethazine
***Course:*** lesions disappear in days to weeks after avoiding contact with the allergen

**Acne and rosacea**
***Oil acne.*** Follicular papules and pustules, mainly on thighs and forearms, due to cutting oils, metal working fluid, grease and lubricating oils.
***Fast-food acne.*** Variant of oil acne, mainly in young individuals exposed to vapours released by grilling and frying

***Acne cosmetic.*** Mainly small non-inflammatory closed comedones, caused by the use of cosmetics, affect, for example, actors, fashion models, beauty specialists.
***Acne mechanica.*** Caused by pressure and friction, e.g. on the back and buttons of drivers.
***Chlor acne.*** Develops in a few weeks after systematic exposure to certain polyhalogenated hydrocarbons.Clinical: a range of lesions, e.g. open comedones and straw-colored cysts.Main localization: cheeks, behind the ears, on the neck, on the buttocks, scrotum and thighs.
***Rosacea.*** Individuals with telangectasia on the face may experience aggravation under hot, humid working conditions. Severe cases may have the appearance of rosacea.

**Psoriasis vulgaris**

***Clinical features*:** Characteristic lesions are sharply demarcated with induration, erythema and scaling. Psoriasis signs: head, ears elbows, knees, natal cleft and nails.
***Pathogenesis*:** hereditary pre-disposition to the development of an inflammatory skin disease with a sub-acute or chronic course. Psoriatic skin lesions have an increase in volume of the epidermis by a factor of 4 to 6 and of the mitotic index by a factor of 8. The renewal of the epidermis is disturbed with an overproduction of normal epidermal cells(hyperkeratosis) and deviant epidermal cells (parakeratosis), probably caused by a disturbed interaction between keratinocytes and T-lymphocytes. The barrier function of psoriatic skin is reduced and external factors, such as shearing and frictional forces, and chemical irritants may induce or aggravate psoriasis.
***Course*:** psoriatic patients have periods when new lesions appear quickly due to exogenous and endogenous factors, e.g. infections of the upper respiratory tract, stress, medication and skin-damaging factors. This phenomenon is known as"endogenous eruption pressure" and is caused by activation of the immune system.
**Remarks:** ***the unaffected skin of psoriatic patients may have a reduced skin barrier, particularly in periods of increased "endogenous eruption pressure", facilitating skin-damaging factors to cause a dermatitis.***

**Leukoderma**

***Clinical features*:** depigmented patches
***Localization*:**fingers, back of the hand, wrists, forearms; may become wore widespread.
***Pathogenesis*:** chemical: cytotoxic effect on the melanocyte.
***Agents*: e.g.** hydroquinone, monomethylether of hydroquinone, p-tert-butylphenol, p-tert-butylcatechol;depigmentation following thermal or chemical burns;post-inflammation: after severe allergic or irritant contact dermatitis
**Remark:** ***leukoderma caused by a cytotoxic effect of melanocytes, is clinically often indistinguishable from idiopathic vitiligo.***

**Hyperpigmentation**
***Clinical features:*** irregular hyperpigmentation, usually sharply demarcated
***Localization:*** arms, legs, face, sometimes covered skin parts.
***Pathogenesis:***Skin burn: chemical or thermal. Post-inflammation:reactive hyperpigmentation after allergic or irritant contact dermatitis, reactive hyperpigmentation after photoallergic or phototoxic contact dermatitis.

**Management of Contact Dermatitis**

Contact dermatitis accounts for at least 90% of all cases of work-related skin diseases. As far as it is distinguished as a work – related case of dermatitis its severity should be assessed. The severity of the disease is classified as follows:
**Grade 1**: Slight dermatitis, no negative effect on the work ability
**Grade 2**: Moderate dermatitis, affecting the work ability, short sick-leave periods may occur
**Grade 3**: Severe dermatitis with restricted work ability and high risk of a long period of sick-leave
Reducing the damaging factor(s) is the propriety when dealing with occupational dermatitis and medical treatment supports the recovery of the skin. Cases of chronic eczema require intense and prolonged medical care. The approach to occupational dermatitis should be based on

- Reduction of exposure to skin damaging factors
- The use of personal protective equipment
- Improving the skin barrier and resistance by medical treatment

While reducing damaging factors targets for the workplace, increasing the resistance of the skin implies medical treatment.
Medical treatment is directed by the severity of the contact dermatitis and existence of endogenous factors, No medication should be chosen which contains skin irritating ingredients or with a negative effect on the skin barrier. This implies avoidance, if possible, of strong topical steroids. The following medication can be used:
**Topical steroids.** Class I or Class II steroids is cream or ointment, Used intermittently to limit side effects. Example: application once or twice a day on four successive days followed by a three day break.
***Remark: Topical steroids may reduce the defense capacity of the skin barrier against irritants***

**Tar preparations.** The main use of tar preparations is in chronic eczema, atopic dermatitis and psoriasis. Tars are not suitable to use in the (sub)-acute forms of dermatitis. Each country has different formulations using coal or wood tar preparations.
**UV-Light therapy.** UVB and PUVA – light therapy is chronic dermatitis or eczema. Especially when atopic dermatitis or psoriasis background is involved.

**Antibiotics.** Eczema is easily colonized by bacteria, particularly Staphylococcus aureus. In mild cases of infection, local antibiotics can be combined with Class I and Class II steroids, Examples: sodium fusidate or mupirocin containing creams. More severe cases of infection should be treated with a suitable oral antibiotic.

**Bland.** Certain ”bland” creams without specific medicaments may promote the healing process by their protective or regenerating effect. The term bland is actually untrue in this context. Knowledge about the use of these protective and regenerative creams is increasing rapidly. Ingredients like petrolatum, ceramides and cholesterol play an important role. The majority of these ointments are supplied by producers who specialize in skin care at the workplace. Distribution, prescribing and reimbursement regulations differ between countries.

# XVIII. LYMPHOPROLIFERATIVE DISORDERS

## 18.1. Cutaneous T-Cell Lymphoma

Cutaneous T-cell lymphoma (CTCL) is a term coined in 1979 to describe a group of lymphoproliferative disorders characterized by localization of neoplastic T lymphocytes to the skin at presentation. The skin is the second most common extranodal site for lymphoma; gastrointestinal sites are first. Of all primary cutaneous lymphomas, 65% are of the T-cell type. The most common immunophenotype is CD4-positive.
These malignancies arise from a distinctive subset of T lymphocytes that normally patrol and home to the skin. Naive T lymphocytes (CD45RA-positive) recirculate from peripheral blood to nodes until they are activated by specific antigens that are presented by dendritic cells in regional draining nodes.
Activated/memory T lymphocytes (CD45RO-positive) that express cutaneous leukocyte antigen (CLA) gain the ability to enter the skin, cycling among 3 compartments, i.e. skin, node, and peripheral blood. CLA, a marker for these cells, is an adhesion molecule that mediates tethering of the T lymphocyte to endothelial cells in cutaneous postcapillary venules via its interaction with E-selectin, found on dermal endothelial cells.

### Classification

The groups of clinicopathologic entities that comprise the CTCLs differ widely in biologic course, histologic appearance, and, in some cases, immunologic and cytogenetic features and response to appropriate treatment.
CTCLs are defined by an integration of these features by 2 classification systems: the European Organization for Research and Treatment of Cancer (EORTC) classification for primary cutaneous lymphomas (1997) and the World Health Organization (WHO) classification of hematologic malignancies (2000).
The EORTC classification focuses on primary cutaneous lymphomas, which may vary from their nodal counterparts in clinical behavior, prognosis, and appropriate therapeutic approaches.
Unlike the general group of lymphomas, a histologic diagnosis in a case of cutaneous lymphoma may not be the final diagnosis but, rather, a differential diagnosis requiring clinicopathologic correlation.
The WHO classification includes cutaneous lymphomas in the general classification of lymphoma to facilitate the description of clinicopathologic entities in their entirety, reporting common features of disease entities that can present in multiple anatomic sites. The WHO classification allows oncologists, dermatologists, and pathologist to use a common language.

## Table 18.1.Comparison of EORTC and WHO-Classifications

| EORTC Classification | Frequency | Five-Year Survival Rate | WHO-Classification |
|---|---|---|---|
| **Indolent Clinical Behavior** | | | |
| Mycosis fungoides (MF) | 40% | 89% | MF |
| MF variants<br>– MF with follicular mucinosis<br>– Pagetoid reticulosis | <br>4%<br><1% | 75% | MF variants<br>☐ MF-associated follicular mucinosis<br>☐ Pagetoid reticulosis<br>☐ Granulomatous slack skin |
| CTCL, large cell, CD30-positive | 10% | 100% | Primary cutaneous CD30-positive lymphoproliferations<br>☐ Anaplastic large cell lymphoma |
| Lymphomatoid papulosis | 14% | 100% | Lymphomatoid papulosis |
| **Aggressive Clinical Behavior** | | | |
| Sézary syndrome | 3% | 11% | Sézary syndrome |
| CTCL, large cell, CD30-negative | 8% | 15% | ☐ Peripheral T-cell lymphoma, unspecified<br>☐ Extranodal natural killer (NK) T-cell lymphoma, nasal type |
| **Provisional Entities** | | | |
| CTCL, pleomorphic, small- or medium-sized | 2% | 62% | |
| Subcutaneous panniculitis-like T-cell lymphoma | 4% | | Subcutaneous panniculitis-like T-cell lymphoma |

Adapted from *Annals of Oncology 2000,* 11 Supplement 1

## 18.1.WHO classification of T-cell and NK-cell lymphomas with frequent or constant cutaneous involvement

•***Primary cutaneous T-cell lymphomas***

- Mycosis fungoides

- Sézary syndrome
- Primary cutaneous anaplastic large cell lymphoma
- Subcutaneous panniculitis-like T-cell lymphoma

•***Other T-cell or NK cell lymphomas with cutaneous involvement***
- Precursor T-lymphoblastic lymphoma leukemia
- T-cell prolymphocytic leukemia
- Aggressive NK cell leukemia
- NK T-cell lymphoma nasal and nasal-type
- Angioimmunoblastic T-cell lymphoma
- Peripheral T-cell lymphoma, unspecified
- Adult T-cell leukemia lymphoma
- Systemic anaplastic large cell lymphoma

## 18.2.Mycosis fungoides/Sézary syndrome

This is the most common CTCL (40%), leading some to use the terms synonymously. Variants of MF recognized by EORTC and WHO include follicular MF and pagetoid reticulosis (Woringer-Kolopp disease).
MF-associated follicular mucinosis manifests with follicular papules, patchy alopecia, and comedo-like lesions. An infiltration of atypical lymphocytes is observed in the epithelium of hair follicles. Treatment with topical treatments may not be effective because of the depth of infiltration.
Pagetoid reticulosis (Woringer-Kolopp disease) manifests with a solitary, asymptomatic, well-defined, red, scaly patch or plaque on the extremities that may slowly enlarge. A heavy, strictly epidermal infiltrate of atypical lymphocytes is observed. The prognosis is excellent, and radiation therapy or surgical excision is the treatment of choice.

## 18.3. Mycosis Fungoides

**Background.**In 1979, the term cutaneous T-cell lymphoma (CTCL) was coined at an international workshop sponsored by the National Cancer Institute. CTCL was used to describe a heterogenous group of malignant T-cell lymphomas with primary manifestations in the skin. In 1806, the term mycosis fungoides (MF) was first used by Alibert, a French dermatologist, when he described a severe disorder in which large necrotic tumors resembling mushrooms presented on a patient's skin. MF is the most common type of CTCL. Sézary syndrome (SS) is a variant of MF, occurring in about 5% of all cases of MF, in which the patient has generalized erythroderma and more than 1000 per $mm^3$ atypical T lymphocytes with cerebriform nuclei circulating in the peripheral blood.
**Pathophysiology.**MF is a malignant lymphoma characterized by the expansion of a clone of $CD4^+$ (or helper) memory T cells that frequently lack other normal T-cell antigens (CD7). These cutaneous lymphocyte antigen (CLA)–positive cells

home to the skin, and some also may retain the ability to exit the skin via afferent lymphatics. They travel to lymph nodes and then through efferent lymphatics back to the blood to join the circulating population of CLA-positive T cells. Then, the disease fundamentally becomes a systemic disease, even when the disease appears to be in an early stage and limited to the skin.

**Mortality/Morbidity.**The overall mortality rate is 0.064 per 100,000 persons; however, the mortality rate widely varies depending on the stage of disease at diagnosis.

•Late-stage MF or SS is associated with declining immunocompetence. Death most often results from systemic infection, especially with *Staphylococcus aureus, Pseudomonas aeruginosa,* and other organisms. Secondary malignancies, such as higher-grade non-Hodgkin lymphoma, Hodgkin disease, colon cancer, and cardiopulmonary complications (e.g. high output failure, comorbid cardiopulmonary disease) also contribute to mortality.

**Age.**The most common age at presentation is 50 years; however, MF also can be diagnosed in children and adolescents with apparently similar outcomes.

**History.*Skin rash***.This may consist of patches, plaques, or tumors, which may have a long natural history.The median duration from the onset of skin symptoms to diagnosis is 6 years. Early in the course of disease, skin lesions may be nonspecific, with a non-diagnostic biopsy result, so confusion with benign conditions is common.Obtain repeated biopsies in those patients who have progressive chronic dermatosis or whose condition is refractory to topical treatments.

***Pruritus, erythroderma***. Often, diagnosis is made possible through the examination of a non-cutaneous site (e.g. blood, lymph nodes).

**Physical.*Skin patch, plaque***.Patch phase MF is characterized by flat, usually erythematous, macules that may have a fine scale, may be single or multiple, and may be pruritic. In dark-skinned individuals, the patches may appear as hypopigmented or hyperpigmented areas. As patches become more infiltrative, they evolve into palpable plaques.Plaques tend to be raised, demonstrating fine-scale, well-demarcated, erythematous shapes with irregular borders. Annular or serpiginous patterns with central clearing and pruritus are common.Patches and plaques may affect any area of the skin, but they often are distributed asymmetrically in the areas that a bathing suit would cover (i.e. hips, buttocks, groin, lower trunk, axillae, and breasts). When the disease affects the scalp, it often is accompanied by alopecia.

Stage IA disease (as defined by the tumor, node, metastases, blood [TNMB] system) is defined as patchy or plaque-like skin disease involving less than 10% of the skin surface area (T1 skin disease).

Stage IB disease is defined as patchy or plaque-like skin disease involving greater than or equal to 10% of the skin surface area (T2 skin disease).

***Skin tumors***.Patients with evidence or a history of patchy or plaque-like skin lesions also can have tumors.Tumors are red-violet nodules that may be dome-

shaped, exophytic, or ulcerated.Stage IIB disease is defined by the presence of tumors (T3 skin lesions).

***Skin erythroderma.***Generalized erythroderma often is intensely symptomatic, with pruritus and scaling that can be profound. The patients experience thickening of the skin folds in the face (leonine facies), hyperkeratosis and fissuring of the palms and soles, onychodystrophy, ectropion of the eyelids, and edema. Sun exposure may be painful as well as pruritic.Stage III disease is defined by the presence of generalized erythroderma.

***Lymph nodes.***Extracutaneous involvement is more clinically evident as the stage and extent of MF increases.Peripheral lymphadenopathy is the most frequent site of extracutaneous involvement in MF.Evaluate palpable lymphadenopathy by obtaining a biopsy because the result influences the patient's stage, prognosis, and treatment.Stage IVA disease is defined by a lymph node biopsy result demonstrating large clusters of atypical cells (i.e.>6 cells [LN3 node]) or showing total effacement by atypical cells (LN4 node).

***Liver, lung***. Stage IVB disease is defined by the presence of visceral involvement (e.g. liver, lung, bone marrow).

**Causes.**Various theories implicate occupational or environmental exposures (e.g.agent orange), other forms of chronic antigenic stimulation, or viral exposures; however, the etiology of MF remains unknown.

**Lab Studies.**Consider HIV and human T-cell lymphotrophic virus type I (HTLV-I) testing. CBC with differential: conduct this test and review the buffy coat smear for Sézary cells.Liver-associated enzyme abnormalities and lactate dehydrogenase (LDH).LDH is a marker of bulky or biologically aggressive disease. Abnormal transaminase values may indicate hepatic involvement. Flow cytometric study of the blood (include available T cell–related antibodies): conduct this test to detect a circulating malignant clone and to assess immunocompetence by quantifying the level of CD8-expressing lymphocytes.Uric acid: perform this study in cases involving a bulky disease and/or biologically aggressive disease.Southern blot testing of the blood: consider this study if detecting a circulating clone of malignant cells in the blood will change medical management.

**Imaging Studies.**Chest radiograph.CT scan of the abdomen and pelvis: perform this test in patients with advanced disease (stage IIB to stage IVB) or in patients with clinically suspected visceral disease.

**Procedures.**Skin biopsy.Perform a punch biopsy, which is formalin fixed for light microscopy. Use a bisected or second punch biopsy on sodium chloride–soaked gauze to allow snap freezing for immunophenotyping and T-cell receptor gene rearrangement.Bone marrow examination: Perform this procedure only if the patient has proven blood or nodal involvement.Lymph node biopsy: Conduct this procedure if the nodes are palpable.

**Histologic Findings.**The criteria for diagnosis include the following: (1) A band-like upper dermal infiltrate of lymphocytes and other inflammatory cells, with no grenz zone, is present;(2) Epidermotropism of mononuclear cells occurs. (3) When a clear halo surrounds an intraepidermal mononuclear cell singly or in clumps, this

is called a Pautrier microabscess. Its presence is suggestive of MF, but it is not necessary for diagnosis. (4) Little spongiosis of the epidermis is found. (5) Lymphocytes have nuclei that are hyperchromatic and convoluted or cerebriform.

**Medical Care.**Conduct the evaluation and treatment on an outpatient basis (usually). Use symptomatic treatments, emollients, or antipruritics in combination with specific topical and systemic treatment.

***Topical treatments***. Generally, use topical steroids, topical chemotherapy (e.g. nitrogen mustard or bischloroethylnitrosourea [BCNU]), ultraviolet B or ultraviolet A treatment enhanced with psoralen [PUVA]), or total body electron beam radiation in the patch or plaque phase. These modalities also are used in the tumor phase combined with systemic modalities (e.g. PUVA plus interferon).

***Systemic treatment.***This treatment is for patients who have relapsed or whose disease is refractory to topical treatments or who have tumors, erythroderma, or nodal or visceral disease.Examples of systemic treatment include the following:

→Extracorporeal photopheresis (leukapheresis with PUVA treatment for the collected white blood cells with reinfusion of treated cells)

→Recombinant alfa interferon

→Oral retinoids

→Fusion toxin treatment

→Systemic chemotherapy with a variety of single agents

***Combination chemotherapy***. This generally is not used because the infectious complications and short response duration outweigh the modest response rates (compared to other non-Hodgkin lymphomas). Increased survival is not demonstrated with the use of combination chemotherapy compared to sequential topical agents.

***Bone marrow transplantation***. Allogenic transplants are reported in the literature as case reports or small groups of patients.

**Complications.**Infection, particularly from indwelling IV catheters.High-output cardiac failure.Anemia of chronic disorders.Edema.Secondary malignancies (skin cancer, melanoma, colon cancer, Hodgkin lymphoma, non-Hodgkin lymphomas).

**Prognosis.**MF and SS are incurable conditions in most patients, with the exception of those with stage IA disease.Mortality and prognosis are related to stage at diagnosis. Patients diagnosed with stage IA disease (patch or plaque skin disease limited to <10% of the skin surface area) who undergo treatment, have an overall life expectancy similar to the age-, sex-, and race-matched controls.Patients who have stage IIB disease with cutaneous tumors or who have stage III disease (generalized erythroderma) have a median survival rate of 3.2 and 4-6 years, respectively.Patients with extracutaneous disease stage IVA (lymph nodes) or stage IVB (viscera) have a survival rate of less than 1.5 years.

**Patient Education.**Encourage the use of supportive treatments to decrease pruritus and lubricate the skin. Avoid sun exposure and remain in a cool environment.

# XIX. HEREDITARY DERMATOSES

## 19.1. Ichthyosis Vulgaris, Hereditary

**Background.**Hereditary ichthyosis vulgaris ichthyosis vulgaris, members of a group of cutaneous disorders of keratinization, appear similar both clinically and histologically. The term ichthyosis is derived from the ancient Greek root *ichthys,* meaning fish. Although the resemblance is rather fanciful, it nevertheless conveys the characteristic features of these diseases. References to ichthyosis have been found in ancient medical texts aged more than 2000 years. Robert Wilan first made the most accurate description of ichthyosis in the English literature in 1808. Later modifications classified the diseases into hereditary and acquired forms.

Hereditary ichthyosis vulgaris is an autosomal dominant genetic disorder first evident in early childhood. It is the most common form of ichthyosis, accounting for more than 95% of ichthyosis cases. It is caused by altered profilaggrin expression leading to scaling and desquamation. Visible scales are retained for longer periods and sloughed off in clumps. Hereditary ichthyosis is also associated with atopy.

**Pathophysiology.**Ichthyosis vulgaris is classified as a retention hyperkeratosis. The only known molecular marker affected by hereditary ichthyosis vulgaris is profilaggrin, a high molecular weight filaggrin precursor. Profilaggrin, synthesized in the granular layer of the epidermis, is a major component of keratohyalin granules. Through various posttranslational modifications, profilaggrin is converted to filaggrin, which aggregates keratin intermediate filaments in the lower stratum corneum. Filaggrin is proteolyzed and metabolized, producing free amino acids that may play a critical role as water-binding compounds in the upper stratum corneum.

Normal expression of the profilaggrin gene can be first detected in the granular layer. In ichthyosis vulgaris, the expression of profilaggrin is absent or reduced in the epidermis. This biochemical abnormality correlates with the decreased numbers of keratohyalin granules and the clinical severity of the condition. Analyses of cultured keratinocytes have shown reduced profilaggrin mRNA. Compared with normal amounts, one study found only 50% of the profilaggrin mRNA and 10% of the profilaggrin protein present. Research has shown that defective posttranscriptional regulation leads to decreased stability of profilaggrin mRNA. The underlying molecular mechanisms accounting for this instability have yet to be determined. Studies using mouse models are currently underway.

**Frequency.**Hereditary ichthyosis vulgaris is a common disease in the United States, with a prevalence of approximately 1 case in 300 persons. Because symptoms improve with age, the true prevalence is probably higher.Hereditary ichthyosis vulgaris is found worldwide, and the prevalence depends on the location.

**Mortality/Morbidity.**Children and adolescents with hereditary ichthyosis vulgaris may experience some morbidity in terms of cosmesis. Secondary infections may occur in fissures of the hands and feet.

**Age.**Hereditary ichthyosis vulgaris typically is absent at birth. It appears in most patients during the first year of life and in the vast majority by age 5 years. The extent of scaling usually intensifies up until puberty and subsequently decreases with age.

**History.**Although the skin in hereditary ichthyosis vulgaris looks and feels normal at birth, it gradually becomes rough and dry in early childhood.

→Scaling tends to be most prominent on the extensor surfaces of the extremities and absent on the flexor surfaces.

→The diaper area is usually unaffected.

→The forehead and cheeks may be involved early on, but scaling usually diminishes in these areas with age.

→A notable amelioration of symptoms occurs during the summer months.

→A family history of hereditary ichthyosis vulgaris may be difficult to ascertain because of the varying degrees of penetrance and the general improvement of symptoms over time.

Many hereditary ichthyosis vulgaris patients have associated atopic manifestations (e.g. asthma, eczema, hay fever). Atopic conditions can be found in many family members, with or without symptoms of ichthyosis vulgaris.

**Physical.**Ichthyosis vulgaris is characterized by symmetrical scaling of the skin, which varies from barely visible roughness and dryness to strong horny plates. Scales are small, fine, irregular, and polygonal in shape, often curling up at the edges to give the skin a rough feel.Scales vary in size from 1 mm to 1 cm in diameter and range from white to dirty gray to brown. Dark-skinned individuals often have darker scales.Different types of scaling may be found in different areas, even in the same patient.Most scaling occurs on the extensor surfaces of the extremities, with a sharp demarcation between normal flexural folds and the surrounding affected areas.The lower extremities generally are more affected than the upper extremities. Compared to other sites, the scales overlying the shins are thicker, darker, and arranged in a mosaic pattern. Patients often report "lizard skin" in these areas during the winter.If the trunk is involved, scaling tends to be more pronounced on the back than on the abdomen.Relative sparing of the face is seen, most likely because of increased sebaceous secretions, although the cheeks and forehead may be involved during early childhood in the hereditary form. Dry scaling is often observed uniformly over the scalp. Sparing of the flexural folds (e.g. neck, axillae, antecubital and popliteal fossae) is attributed to the relative increase in temperature and humidity in these areas. Overall symptoms of ichthyosis vulgaris generally improve in the summer months or in warm climates. Hyperkeratosis is often present on the palms and soles, causing them to appear dirty.Skin creases in these areas are more prominent and can lead to painful fissuring, especially during dry weather. Secondary infections at fissure sites are common.

Keratosis pilaris (follicular hyperkeratosis) occurs on the side of the cheek and neck, dorsum of the upper arms, buttocks, and thighs. It consists of spiny parafollicular papules that when palpated resemble a cheese grater. Dried skin in the central portion is often white and mistaken for pus. Inflammation may or may not be present. Keratosis pilaris, which can be present without scaling, may be the only finding in family members with hereditary ichthyosis vulgaris.Pruritus can be caused by dry skin, even if inflammation is not evident. As a result, itching and scratching may lead to erythema in affected areas.

**Causes.**Hereditary ichthyosis vulgaris is an autosomal dominant genetic disorder first evident in early childhood.

**Procedures.**Skin biopsy specimens can be examined under light microscopy and electron microscopy. Take biopsy samples from regions of maximal hyperkeratosis because areas of mild scaling are less reliable for histopathologic analysis and findings may be indistinguishable from those of normal skin. The thickest scales are usually found on the anterior aspect of the lower leg.

**Histologic Findings.**The histological appearance of both hereditary ichthyosis is practically identical. The stratum corneum shows compact hyperkeratosis, although some areas can be laminated. Patchy parakeratosis and occasional follicular plugging is seen. The granular layer is usually one-layer thick or absent. The stratum malpighii is usually intact but has a decreased rete-papillae pattern. The eccrine and sebaceous glands, when present, are small, atrophic, and reduced in number. Sweat glands and hair follicles are evident. Most patients have a slight, perivascular, lymphohistiocytic infiltration in the upper dermis. Ichthyosiform sarcoid, a manifestation of acquired ichthyosis in sarcoid patients, has the additional presence of multiple non-caseating granulomas in the dermis.

Ultrastructural studies show reduced or absent keratohyalin granules housed in the granular layer. They appear spongy or crumbly, most likely due to defective keratohyalin synthesis. The hyperkeratotic portions of the stratum corneum have a normal keratin pattern.

**Medical Care.**Hereditary ichthyosis vulgaris is a chronic disorder that may improve with age but often requires continuous therapy. The main approach to treatment of both conditions includes hydration of the skin and application of an ointment to prevent evaporation. Hydration promotes desquamation by increasing hydrolytic enzyme activity and the susceptibility to mechanical forces. Pliability of the stratum corneum is also improved.

Alpha-hydroxy acids (e.g. lactic, glycolic, or pyruvic acids) are effective for hydrating the skin. They work by causing disaggregation of corneocytes in the lower levels of the newly forming stratum corneum. Lactic acid is available as a 12% ammonium lactate lotion, or it can be compounded by prescription in a concentration of 5-10% in a suitable vehicle. Twice-daily applications have shown to be superior to petrolatum-based creams for controlling of ichthyosis vulgaris.

Removal of scales can be aided by keratolytics (e.g. salicylic acid), which induce corneocyte disaggregation in the upper stratum corneum. A commercially available 6% salicylic acid gel can be used as needed.

Over-the-counter products often contain urea or propylene glycol. Moisturizers containing urea in lower strengths (10-20%) produce a more pliable stratum corneum by acting as a humectant. Propylene glycol draws water through the stratum corneum by establishing a water gradient. Thick skin is then shed following hydration. Propylene glycol is a common vehicle in both prescription and over-the-counter preparations.
Topical retinoids (e.g. tretinoin) may be beneficial. They reduce cohesiveness of epithelial cells, stimulate mitosis and turnover, and suppress keratin synthesis. Tazarotene, a topical receptor-selective retinoid, has also been effective in one small trial.
**Prognosis.**The prognosis for hereditary ichthyosis vulgaris is excellent. Many patients experience improvement of symptoms with age.

## 19.2. Ichthyosis, Lamellar

**Synonyms and related keywords:** non-bullous congenital ichthyosiform erythroderma, non-bullous congenital ichthyosiform erythroderma, autosomal recessive ichthyosis, erythrodermic autosomal recessive lamellar ichthyosis.

**Background.**Lamellar ichthyosis is an autosomal recessive disorder that is apparent at birth and is present throughout life. The newborn is born encased in a collodion membrane that sheds within 10-14 days. The shedding of the membrane reveals generalized scaling with variable redness of the skin. The scaling may be fine or plate-like, resembling fish skin. Although the disorder is not life threatening, it is quite disfiguring and causes considerable psychological stress to affected patients.
**Pathophysiology.**Patients with lamellar ichthyosis have accelerated epidermal turnover with proliferative hyperkeratosis, in contrast to retention hyperkeratosis. This involves a mutation in the gene for transglutaminase 1 (*TGM1*). The transglutaminase 1 enzyme is involved in the formation of the cornified cell envelope.
**Causes.**Lamellar ichthyosis is an autosomal recessive disorder in almost all cases. Genetic linkage studies have been performed on families with classic lamellar ichthyosis and show markers on band 14q11 in the region of the *TGM1* gene locus. An autosomal dominant form of lamellar ichthyosis has been described.
**Mortality/Morbidity.**In the neonatal period, following the shedding of the collodion membrane, the newborn is at risk for secondary sepsis and hypernatremic dehydration. As the child ages, the hyperkeratosis can interfere with normal sweat gland function, which can predispose to heat intolerance and possible heat shock. Ectropion may result in the inability to fully close the eyelids and can cause exposure keratitis.
**Age.**The disease is present at birth and continues throughout life.

**Physical.*Newborn period***. The newborn presents encased in a tough, film-like membrane that fissures when stretched. This collodion membrane is shed by 10-14 days, revealing generalized erythema and scaling.

***Childhood and adulthood.Skin***. The disease is characterized by generalized scales, which range from fine and white to thick, dark, and plate-like. The scales are arranged in a mosaic pattern resembling fish skin. The lesions involve the entire body and are increased in flexural surfaces such as the axilla, groin, antecubital fossa, and neck. The individual scales tend to be larger over the legs and, in some areas, are centrally attached and raised at the edges.

***Nail abnormalities***. These include secondary dystrophy with nail fold inflammation, subungual hyperkeratosis, and longitudinal or transverse stippling. The nails may grow 2-3 times the normal rate.

***Scalp***. Scarring alopecia can result from the overall tightness of skin and the thick stratum corneum entrapping hairs. The hair may be thin and fine but, similar to the nails, can grow at 2-3 times the normal rate.

***Other findings***. The lips and mucous membranes tend to be spared. Other associated features are ectropion, eclabium, bilateral conjunctivitis, small and deformed ears, and inflexible digits due to taut skin.

**Lab Studies.**As a result of the abnormal skin barrier, neonatal sepsis is a significant risk in the newborn period. If sepsis is considered, perform a sepsis workup. Chemistries and fluids need to be monitored closely because of the high incidence of hypernatremia observed.

**Procedures.**Skin biopsies can aid in the diagnosis of lamellar ichthyosis. At birth, electron microscopy can be used to differentiate a severe collodion baby affected by lamellar ichthyosis from a baby affected by harlequin ichthyosis by demonstrating the absence of the marginal band.

**Histologic Findings.**Skin biopsy results show a normal or thickened granular layer, mild-to-moderate hyperkeratosis with increased mitoses, and a perivascular lymphocytic infiltrate. In autosomal dominant lamellar ichthyosis, the stratum granulosum and stratum corneum are separated by a prominent transforming zone and scales contain elevated triglyceride and fatty acid levels, which aids in differentiation from autosomal recessive lamellar ichthyosis.

**Surgical Care.**Surgery is occasionally necessary for severe ectropion.

**Consultations.**Consult a dermatologist for the evaluation and treatment of the skin. Consult an ophthalmologist for the evaluation and management of ectropion from birth. Consult a genetics counselor for a discussion of the risks of subsequent children being affected.

**Activity.**A potential for heat intolerance and heat stroke is present; however, with proper counseling, activity does not need to be limited.

**Medical Care.**This disorder has no cure; therefore, treatment is directed at decreasing symptoms. Emollients should be applied after showering or bathing. The stratum corneum can absorb 6 times its weight in water, and a heavy emollient, such as petrolatum jelly (Vaseline) or water-in-oil preparations (e.g. Eucerin) should be applied while the skin is still wet. Alpha-hydroxy acids, such as

lactic acid (e.g. Lac-Hydrin), help reduce corneocyte adhesion and decrease the thickness of the epidermis. Urea creams can help soften scales. Salicylic acids in combination with propylene glycol help to remove dark scaling. Care must be taken when using topical salicylates over large areas, especially in children, because of reports of systemic salicylate intoxication. Topical retinoic acids (e.g. Retin-A) decrease thickened scaling. Antiseptics and antimicrobials can be used topically to control odor. Because of the significant long-term adverse effects, reserve systemic retinoids for severe disease that is refractory to conventional therapy. Newer therapies that have resulted in clinical improvement are Locobase fatty cream, which is 5% lactic acid and 20% propylene glycol in a lipophilic cream base; topical *N*-acetylcysteine, which has an antiproliferative effect; tazarotene topical 0.05%, a receptor-selective retinoid; and calcipotriol, a synthetic derivative of vitamin D-3.

**Transfer** the newborn to the neonatal intensive care unit for close monitoring of fluids, electrolytes, and signs of sepsis. Manual debridement of the collodion membrane is not recommended.

**Prevention.**Prenatal diagnosis is controversial. A fetal skin biopsy at 22 weeks may aid in prenatal diagnosis. In patients with a known gene locus, DNA linkage analysis may be useful.

**Prognosis.**Patients with lamellar ichthyosis have normal life spans.

## 19.3. Epidermolytic Hyperkeratosis (Bullous Congenital Ichthyosiform Erythroderma)

**Synonyms and related keywords:** bullous congenital ichthyosiform erythroderma

**Background.**Epidermolytic hyperkeratosis (EHK) also is termed bullous congenital ichthyosiform erythroderma. EHK is a rare autosomal dominant ichthyosis, yet a high frequency of spontaneous mutations (up to 50%) occurs. In 1902, Brocq first described it as bullous ichthyotic erythroderma to distinguish the entity from congenital ichthyotic erythroderma.

**Pathophysiology.**The defect is found in the genes for keratin 1 and keratin 10. Keratins are divided into 2 classes including basic type II keratins and acidic type I keratins. Keratin 1 is one of the basic type II keratins found on chromosome 12; keratin 10 is one of the acidic type I keratins found on chromosome 17. Keratins form intermediate filaments when both type I and type II keratins are present. This combination provides structural stability to keratinocytes. Keratins 1 and 10 are coexpressed and are involved in the suprabasilar differentiation of keratinocytes. A defect at this level (as in EHK) weakens the structural stability of the keratinocytes, causing easy blistering, hyperproliferation, and hyperkeratosis.

**Causes.**Defects in genes for keratin 1 and 10 are the cause of EHK. Defects in keratin 1 are associated with the PS variants; defects in keratin 10 are associated with the NPS variants.

**Frequency.**1 case per 200,000-300,000 persons.

**Mortality/Morbidity.**Mortality is possible if sepsis or electrolyte imbalance is not treated properly during the neonatal period. Morbidities include recurrent infection, sepsis, and electrolyte imbalance, which are possible during the neonatal period.
**Age.**EHK is a lifelong condition with an onset at birth or in the neonatal period.
**History.**EHK presents at birth or shortly thereafter as erythema, blistering, and/or peeling, but symptoms in some patients may ameliorate over time.
**Physica.**In 1994, DiGiovanna and Bale separated the various clinical presentations of EHK into 2 primary types, including NPS (without severe palm/sole hyperkeratosis) and PS (with severe palm/sole hyperkeratosis) based on the presence or absence of severe palmoplantar hyperkeratosis. The 2 primary types were subdivided further into 3 subtypes each depending on the clinical presentations. Some of the subtypes have general involvement, while others are localized only.
***NPS subtypes*** do not have severe palmoplantar involvement. Distinctions between the 3 NPS subtypes are based on different clinical presentations.**NPS-1** has normal palmoplantar surfaces, no digital contractures, a hystrix scale, a generalized skin distribution, no history of erythroderma, a positive history of blistering, and patients may have abnormal gait.**NPS-2** is similar to NPS-1. The only differences are a brown scale instead of a hystrix scale and a lack of gait abnormalities.**NPS-3** has no palmoplantar hyperkeratosis, no digital contractures, and is generalized in skin distribution similar to NPS-1 and NPS-2. In contrast, the palmoplantar surface in NPS-3 is hyperlinear, has minimal scale, and a thin white scale is most prominent on the trunk. Erythroderma is mild to moderate. NPS-3 may have gait abnormalities similar to NPS-1.
***PS subtypes*** have severe palmoplantar involvement. The 3 subtypes are differentiated based on clinical presentations.**PS-1** has smooth palmoplantar hyperkeratotic surfaces, no digital contractures, a localized distribution of skin involvement (limited flexural involvement, truncal sparing), no erythroderma, a localized blistering, and no gait abnormalities.**PS-2** has smooth palmoplantar hyperkeratotic surfaces but has digital contractures, generalized skin involvement with hyperkeratosis most severe over the joints at both flexor and extensor surfaces, mild-to-moderate erythroderma, positive blistering, and may have gait abnormalities.**PS-3** has cerebriform palmoplantar surfaces, no digital contractures, a tan scale, generalized skin involvement, no erythroderma, neonatal blistering, and no gait abnormalities.
**Complications.**Patients are at an increased risk for recurrent infections, and a pungent smell can be noted.
**Lab Studies.**No general laboratory studies are needed, except if necessary to follow chosen therapy or bacterial culture for suspected infection. Keratin defect studies can be performed.
**Procedures.**Along with clinical presentation and history, biopsies can be diagnostic in de novo cases.Keratin studies can be performed.Prenatal diagnosis can be made through analysis of chorionic villus sampling, amniotic cells, or fetal skin biopsies.

**Histologic Findings.**Hematoxylin and eosin findings are distinctive but not unique. Typical findings include marked hyperkeratosis, thick granular layer, coarse keratohyaline granules, vacuolar degeneration of the upper dermis. Occasionally, deeper granular cells become dense, enlarged, and irregular, and the shaped masses appear to be keratohyaline granules. Electron microscopy findings show clumping of keratin filaments beginning at the suprabasal layer.
**Medical Care.**Correct diagnosis is the first step in this genodermatosis. Genetic counseling and prenatal diagnosis also can be offered. Newborns with denuded skin are at increased risk for infection, secondary sepsis, and electrolyte imbalance. These newborns should be transferred to the neonatal intensive care unit (NICU) to be monitored and treated as needed. Since the condition tends to improve with time, visits to the physician decrease. Wound care for blistering and aggressive moisturization/emollients are important.
**Consultations.**Refer patients who are considering conceiving children to a geneticist for reproductive concerns and assistance.Prenatal diagnosis can be made by ultrastructural analysis and by direct gene sequencing.Prenatal diagnosis of EHK can be performed by ultrastructural analysis of fetal skin biopsies and amniotic fluid cells. Keratin 1 and keratin 10 are expressed suprabasally as early as week 14 of gestation; normal fetal keratinization does not begin until the 24th week. To date, keratin filament aggregates have been detected for diagnostic purposes in the 19th week of gestation for diagnosis.Chorionic villus sampling can diagnose EHK earlier by direct gene sequencing if the familial mutation is known. The earliest documented diagnosis by this method is at the 15th week of gestation, but the chorionic villus sampling theoretically can be tested as early as the eighth week of gestation.
**Diet.**No special diet is needed. Reports of improvement have been noted with high-dose beta carotene, systemic retinoids, topical retinoids, 10% glycerin, lactic acid, alpha-hydroxy acid, calcipotriol, antibacterial soap, and urea.
**Further Inpatient Care.**Neonatal patients may need to be transferred to the NICU for monitoring of infection, sepsis, electrolyte imbalance, and administration of intravenous fluids or antibiotics.
**Prognosis.**EHK is a lifelong condition. Some patients may experience amelioration of symptoms as they age.
**Patient Education:** Educate patients concerning the potential of passing the chromosomal defect on to offspring.

## 19.4. Ichthyosis, X-Linked

**Synonyms and related keywords:** ichthyosis nigricans, x-linked ichthyosis
**Background:** In 1965, Wells and Kerr first recognized X-linked ichthyosis (XLI) as a distinct entity by studying its characteristics in 81 affected males. XLI is the second most common type of ichthyosis and one of the most frequent human enzyme deficiency disorders. XLI is a clinically mild genetic disorder of

keratinization, with extracutaneous manifestations in some cases. It is caused by a steroid sulfatase (STS) deficiency resulting from abnormalities in its coding gene (*STS*). The 2 best-known substrates for this microsomal enzyme are cholesterol sulfate (CSO4) and dehydroepiandrosterone sulfate. Approximately 90% of patients with XLI have complete or partial deletions of the *STS* gene. No evidence of genotypic-phenotypic correlation has been shown, regardless of the location or type of the *STS* mutation.

The 2 molecular pathways that may contribute to XLI pathogenesis are (1) excess CSO4 producing non-lamellar phase separation in the stratum corneum interstices, explaining the barrier abnormality, and (2) the increased CSO4 in the stratum corneum interstices sufficiently inhibiting activity to delay CD degradation, leading to corneocyte retention.

**Pathophysiology.**Retention hyperkeratosis results from the delayed dissolution of desmosomes in the stratum corneum. COS4 is a multifunctional sterol metabolite, produced in large amounts in squamous keratinizing epithelia. It may be both a marker for squamous metaplasia and an inducer of differentiation. STS acts upon COS4, which is a product discharged by the Odland bodies of the granular layer. Since STS is missing in XLI, it cannot act on COS4, resulting in persistent cellular adhesion and reduced normal desquamation. Patients with XLI have a 10-fold increase in COS4 levels and a 50% reduction in cholesterol levels. Recent work suggests that COS4 accumulation, rather than cholesterol deficiency, is responsible for the barrier abnormality.

Since 1978, a deficiency in the STS enzyme has been known to be responsible for the abnormal cutaneous scaling. The *STS* gene has been mapped to the distal part of the short arm of the X chromosome (band Xp22.3). This region escapes X-chromosome inactivation and has the highest ratio of chromosomal deletions among all genetic disorders. Complete or partial deletions have been found in as many as 90% of patients. Deletion of the entire *STS* gene is the most common molecular defect found in patients with XLI. The large deletions of the *STS* gene are generated by inaccurate recombination at the *STS* locus. Additional flanking sequences are usually missing as well. The *STS* gene has 10 exons and spans more than 146 kilobases of DNA. Its introns vary considerably in size. It is transcribed into messenger RNA and translated into a protein of 561 residues.

**Causes.**XLI is a genetic disorder caused by STS deficiency that results from abnormalities in its coding gene.

**Frequency.**XLI is a relatively common disease, affecting approximately 1 in 6000 males worldwide, with no geographic or racial variations. The frequency of XLI was estimated to be approximately 1.98 cases per 10,000 males, which is similar to estimates from other European surveys.

**Mortality/Morbidity.**Clinically, XLI is usually a relatively mild eruption that rarely can be emotionally challenging for children and adolescents. Most patients perceive it as more of an annoyance than a serious medical problem.

**Sex.**Males are affected overwhelmingly; however, a few female heterozygotes have been reported. XLI was described in 3 homozygous women who were daughters of a father with the disorder and a mother who was a carrier.
**Age.**XLI occurs at birth or in early infancy. It may become more prominent as the child ages.
**History.**XLI is seen at birth or in the immediate neonatal period. Most typically, XLI appears in infancy with scaling on the posterior neck, upper trunk, and extensor surfaces of the extremities. The scalp is often involved.In childhood, the boy who is affected has a "dirty-face" appearance, with an increase in involvement with age.
**Physical.**Adherent brown scaling is evident in a widespread distribution that often produces a dirty-face appearance.In early childhood, scaling of the scalp, preauricular skin, and posterior neck may be prominent.Flexures may be involved, but palms and soles are usually spared. As the child ages, the mild scaling evident in the first few days of life becomes more evident and assumes a dirty yellow or brown color with dark, polygonal, firmly adherent scales.This generalized eruption tends to fade on the head but becomes more prominent on the trunk and extremities, particularly on the extensor surfaces of the legs.Scaling has a tendency to be more noticeable in cold and dry weather, improving in the summer months.Hair and nails are normal in XLI. Corneal opacities may be evident with slit-lamp examination both of adults who are affected and of women who are carriers. The flowerlike opacities in the posterior stroma are common findings. Approximately 10% of males who are affected and female carriers have diffuse deposits in the posterior capsule or corneal stroma that does not affect vision. Cryptorchidism occurs in 20% of patients. A few cases of testicular cancer have developed in patients with XLI and cryptorchidism.Central nervous system electroencephalographic changes have been noted in a few patients.STS deficiency slows the delivery of an infant because of insufficient cervical dilation. A relative failure occurs in the response to intravenous oxytocin. Since both are indications for cesarean delivery or forceps delivery, an increased perinatal morbidity and mortality may occur.
Syndromes of genetic contiguity have been described. As a result of broader chromosomal deletions, they may have XLI and additional phenotypical abnormalities, which include short stature, chondrodysplasia punctata, mental retardation, and Kallmann syndrome (hypogonadotrophic hypogonadism).
**Lab Studies:** Diagnosis of patients with XLI and female carriers is based on biochemical and genetic analysis. Genetic analysis currently is the most accurate diagnostic method in most patients. XLI can be diagnosed by assaying STS activity in the placenta or in the skin fibroblasts, keratinocytes, or lymphocytes of patients after birth. Patients show a deficiency of arylsulfatase C, which can be demonstrated by biochemical testing. Polymerase chain reaction (PCR) and Southern blot testing are useful for the genetic diagnosis of XLI, although a few patients with XLI carrying point mutations rather than deletions may be missed. PCR is not applicable for carrier detection.XLI can be diagnosed prenatally using

fluorescence in situ hybridization. Maternal peripheral blood metaphase spreads may display 2 hybridization signals on one of the X chromosomes (1 in the *STS* region [band Xp22.3] and 1 in the centromeric region), but only 1 hybridization signal (in the X centromeric region) on the other X chromosome; therefore, one of the X chromosomes has a deletion in the band Xp22.3 region, a result consistent with the carrier status for STS deficiency and XLI. In metaphase spreads from amniotic fluid samples, the X chromosome shows 1 hybridization signal in the control region, but no hybridization signal in the *STS* region. Therefore, the X chromosome of this male fetus has a deletion in the *STS* region, a result consistent with XLI. The deficit in placental STS blocks placental steroid synthesis, resulting in excretion of maternal urinary steroids in much lower amounts than normal.

Incorporating unconjugated estriol in maternal serum into the calculation of risk increases the yield of screenings performed during pregnancy for detection of fetal chromosomal and structural anomalies.

The differential diagnosis of low and undetectable levels of unconjugated estriol in maternal serum includes XLI and serious fetal pathologies (e.g. adrenal insufficiency, anencephaly, Down syndrome). To diagnose XLI, examine the urine of these pregnant women for low levels of nonhydrolyzed sulfated steroids.

**Histologic Findings.**Histologic changes of XLI often are subtle. Biopsy specimens from ichthyotic skin with mild scaling may appear normal. Specimens obtained from regions of thick scaling (e.g. anterior aspect of legs, extensor aspect of arms) show mild-to-moderate compact laminated eosinophilic orthokeratotic hyperkeratosis, with a normal or slightly thickened granular layer 3-4 cells thick, mild acanthosis, well-preserved rete ridges, and a sparse perivascular and periappendageal lymphohistiocytic infiltrate.

Ultrastructurally, keratohyaline granules are increased in size and number. Normal-appearing keratinocytes appear linked by desmosomal disks all the way up into the stratum corneum, where the anucleated cells have increased numbers of melanosomes, which may account for the dark coloration of scaling in XLI.

**Treatment.**Topical keratolytics, emollients, and hydrating agents are used to reduce scaling.Topical isotretinoin may be beneficial. In a small study, the topical receptor-selective retinoid tazarotene was efficacious.

***Surgical Care*:** In cases with cryptorchidism, consider surgical intervention if spontaneous descent has not occurred by age 1 year.

**Consultations.**An ophthalmologist may detect corneal opacities. An obstetrician should be involved for higher risk delivery in future pregnancies.

**Further Outpatient Care:** Address the risk for testicular carcinoma by monitoring patients with periodic physical examinations.

**Prognosis:** XLI is a clinically mild genetic disorder. Some morbidity may occur in terms of cosmesis for adolescent boys.

## 19.5. Keratosis Palmaris et Plantaris

Palmoplantar keratoderma (PPK) constitutes a heterogeneous group of disorders characterized by thickening of the palms and the soles of individuals who are affected. The condition may be subdivided into hereditary forms, acquired forms, and syndromes with PPK as an associated feature.
Hereditary forms may be localized to the hands and the feet, or they may be associated with a more generalized skin disorder. Classification of hereditary PPK is frequently confusing, and a simple working classification is outlined below. This classification incorporates 3 factors: (1) the specific morphology and distribution of the palmoplantar keratosis, (2) the presence of associated cutaneous and non-cutaneous ectodermal disease in sites other than the palms and the soles, and (3) the presence or absence of histologic epidermolysis. A diffuse pattern of PPK describes uniform involvement of the palmoplantar surface. Focal keratosis refers to localized areas of hyperkeratosis located mainly on pressure points. Punctate keratoderma features small, hyperkeratotic papules, spicules, or nodules on the palms and the soles.

### Diffuse Hereditary PPK without Associated Features

#### Diffuse non-epidermolytic PPK

Synonyms include diffuse NEPPK, Thost-Unna disease, and PPK diffusa circumscripta. Diffuse non-epidermolytic palmoplantar keratoderma is inherited in an autosomal dominant fashion. It often presents within the first 2 years of life.
***Clinical features*** include the following:

- Even, thick, diffuse hyperkeratosis is present over the palms and the soles.
- Red band at the periphery of the keratosis is frequent.
- Aberrant keratotic lesions may appear in the dorsum of the hands, the feet, the knees, and the elbows.
- Hyperhidrosis may be present.
- Nails may be thickened.

***Histologic findings*** include orthokeratotic hyperkeratosis associated with hypergranulosis or normogranulosis and moderate acanthosis. Changes are nonspecific and common to many varieties of keratoderma.
***Molecular biology features*** include linkage to type II keratin locus on band 12q11-13. K1 gene mutation was reported in a single family.
***Treatment***includes the following: topical keratolytics, such as 6% salicylic acid in white soft paraffin or a gel of 6% salicylic acid in 70% propylene glycol; benzoic acid compounds; and oral retinoids.

#### Diffuse epidermolytic PPK

Synonyms include diffuse EPPK, Vorner disease, and PPK cum degeneratione granulosa. This form is the most common type of hereditary PPK. It is inherited in an autosomal dominant fashion. Onset occurs within the first year of life.

***The clinical features are phenotypically similar to NEPPK.***
***Thehistologic features*** are characterized by epidermolytic hyperkeratosis, which differentiates it from NEPPK.
***Molecular biology features*** include a mutation in the highly conserved 1A rod domain segment of the keratin 9 gene on chromosome 17.
***Treatment*** includes oral retinoids and topical calcipotriol.

**Progressive PPK**
Synonyms include PPPK, Greither disease, and PPK trangrediens et progrediens. Progressive PPK is inherited in an autosomal dominant fashion. Onset occurs in children aged 8-10 years.
***Clinical features*** include the following:
- Diffuse PPK extends onto the dorsa of the hands and the feet (trangrediens), with characteristic involvement of the Achilles tendon.
- Hyperhidrosis and intrafamilial phenotypic variation are common.
- The condition tends to be worse during childhood, static after puberty, and improves in the fifth decade of life.

***The histologic features*** are nonspecific, with orthohyperkeratosis and absence of granular cell degeneration.

**Palmoplantar keratosis Gamborg-Neilson**
Synonyms include Gamborg-Nielson keratoderma. Palmoplantar keratosis Gamborg-Neilson is inherited in an autosomal recessive fashion.
***Clinical features*** include the following:
- Severe form of PPK has been delineated in 2 families with 6 patients in Sweden.
- Thick, diffuse keratoderma with knuckle pads and occasional keratosis on the dorsa of the hands has been described.
- Mutilating changes due to constricting bands surrounding the fingers have also been described.

**Diffuse Hereditary PPK with Associated Features**

Diffuse PPK is associated with extrapalmoplantar skin involvement in several inherited disorders of keratinization. The more common conditions are outlined below.

**Mal de Meleda**
Synonyms include keratosis extremitatum hereditaria trangrediens et progrediens. This condition is rare. The prevalence is 1 case in 100,000 population. Initially, it was described in inhabitants of the Adriatic Island of Meleda (Miljet).
Mal de Meleda is inherited in an autosomal recessive fashion. Onset occurs in early infancy.
***Clinical features*** include the following:

•Diffuse, thick keratoderma with a prominent erythematous border that spreads onto the dorsa of the hands and the feet
•Constricting bands around digits resulting in spontaneous amputation
•May have well-circumscribed psoriasis-like plaques or lichenoid patches on the knees and the elbows
•Hyperhidrosis
•Periorbital erythema and hyperkeratosis
•Nail changes (koilonychia, subungual hyperkeratosis)
•Lingua plicata, syndactyly, hair on the palms and the soles, high arched palate, and left-handedness (These are all associated features.)
***Molecular biology features*** include linkage analyses in 2 large families that have shown strong evidence of localization to 8qter.
***Treatment*** includes oral retinoids.

**PPK mutilans Vohwinkel**
Synonyms include mutilating keratoderma, Vohwinkel syndrome, and palmoplantar keratoderma mutilans. PPK mutilans Vohwinkel is inherited in an autosomal dominant fashion. Onset occurs in infancy.
***Clinical features*** include the following:
•This condition presents in infants as a honeycomb-like keratosis of the palms and the soles.
•Later-forming, constricting, fibrous bands appear on the digits and lead to progressive strangulation and autoamputation.
•Starfish-shaped keratosis may occur on the dorsa of the fingers and the knees.
•Alopecia, deafness, spastic paraplegia, myopathy, ichthyosiform dermatosis, and nail abnormalities are associated.
***Molecular biology*** includes a loricrin gene mutation (1q21).
***Treatment*** includes oral retinoids.

**Mutilating PPK with periorificial keratotic plaques**
Synonyms include Olmsted syndrome. This condition is inherited in an autosomal dominant fashion. Onset occurs in the first year of life.
***Clinical features*** include the following:
•Symmetric, sharply defined PPK surrounded by erythema with flexion deformities of the digits lead to constriction and spontaneous amputation.
•Periorificial keratosis
•Onychodystrophy
•Perianal involvement, variable leukokeratosis
***Treatment*** includes etretinate and topical tretinoin.

**PPK with sclerodactyly**
Synonyms include Huriez syndrome. PPK with sclerodactyly is inherited in an autosomal dominant fashion. Onset occurs in infancy.

***Clinical features*** include the following: sclerodactyly, diffuse keratoderma more marked on the soles than the palms, nail abnormalities, hypohidrosis,associated with squamous cell carcinoma.

***Histologic findings*** include the following:

- A biopsy sample of keratoderma shows acanthosis, accentuation of the granular layer, and orthohyperkeratosis.
- On electron microscopy, dermoepidermal junctions and desmosomes are normal; however, dense bundles of tonofilaments are seen in the epidermal layer. The granular layer shows large, coarse, clumped keratohyalin.
- A biopsy sample of the scleroatrophic area shows similar changes with thinning of the elastic fibers.

**PPK with periodontitis**

Synonyms include Papillon-Lefèvre syndrome. The frequency of PPK with periodontitis is 4 cases per 1 million population. This condition is inherited in an autosomal recessive fashion. The male-to-female ratio is equal. Onset occurs in the first and fifth year of life.

***Clinical features*** include the following:

- Diffuse trangrediens palmoplantar keratosis may be observed.
- Unless treated, periodontosis results in severe gingivitis and loss of teeth by age 5 years.
- Patients exhibit increased susceptibility to infection.
- This possibly is a disorder of leukocyte function, which accounts for prominent gingival and cutaneous infections.
- Some reports suggest a disturbance in leukocyte motility and bacteriocidal function that causes recurrent infections.
- Scaly, erythematous lesions are often observed over the knees, the elbows, and the interphalangeal joints.
- Hyperhidrosis and malodor may be present.

***Histologic findings*** include the following:

- Findings are nonspecific, but evidence of hyperkeratosis with irregular parakeratosis and moderate perivascular infiltration exists.
- Electron microscopic features include lipid-like vacuoles in corneocytes and granulocytes, a reduction in tonofilaments, and irregular keratohyalin granules.

***Molecular biology findings*** include the following:

- Gene locus is mapped to band 11q14-q21.
- Cathepsin C gene is of possible importance.

***Treatment*** includes dental clearance and appropriate antibiotic therapy for periodontitis and oral retinoids.

**Hidrotic ectodermal dysplasia**

Synonyms include Clouston syndrome. Hidrotic ectodermal dysplasia is inherited in an autosomal dominant fashion.

***Clinical features*** include the following: diffuse, papillomatous PPK;dystrophy of the nails, universal sparsity of hair;sensorineural deafness, polydactyly, syndactyly, finger-clubbing, mental retardation, dwarfism, photophobia, and strabismus are associated. Biochemically, depletion of hair matrix protein may account for clinical features.

***Molecular biology*** findings: Clouston syndrome is mapped to band 13q11-q12.1.

**Treatment** of all types of hereditary and keratodermas is difficult. The most known therapeutic options only result in short-term improvement and are frequently compounded by unwanted adverse effects. Treatment tends to be symptomatic and may vary from simple measures, such as saltwater soaks and paring, to topical keratolytics, systemic retinoids, or reconstructive surgery with total excision of the hyperkeratotic skin followed by grafting. The mainstays of treatment include the following. The use of topical keratolytics is common, particularly in patients with limited keratoderma. Examples include 5-10% salicylic acid, 10% lactic acid, or 10% urea in a suitable base. Topical retinoids, such as tretinoin (0.01% gel and 0.1% cream), are effective, but treatment is often limited by skin irritation. Consider potent topical steroids with or without keratolytics in dermatosis with an inflammatory component. Treatment with 5% 5-fluorouracil has produced dramatic results in spiny keratoderma, but its use in other keratodermas has not been evaluated. Oral retinoids are effective, especially in some hereditary PPKs, such as mal de Meleda, Papillon-Lefèvre syndrome, and erythrokeratoderma variabilis. Most hereditary PPKs require long-term treatment. Results indicate that acitretin is comparable to etretinate. Intermittent therapy should be attempted whenever possible. To limit unacceptable long-term adverse effects, the optimal dosage of acitretin in adults is 30-35 mg/d (0.5-1 mg/kg/d for adults and 0.5 mg/kg/d for children). Treatment of women of childbearing age results in long-term potential teratogenic effects. The maintenance dose can be reduced to 25 mg/d. Caution is advised if the patient has an epidermolytic form because large erosions may occur with retinoid therapy. Patients should be started on a low dose, and the dosage should be carefully increased to avoid flaring the disease and/or causing erosions.

Specific therapies dependent on the PPK type may be used. Psoralens and ultraviolet A (PUVA) or re-PUVA (a combination of oral retinoids and PUVA) may be indicated in PPK secondary to psoriasis or eczema. Patients with oculocutaneous tyrosinemia may benefit from dietary restriction of phenylalanine and tyrosine. Improvement has been seen in nonhereditary PPK after oral 1-alpha, 25-dihydroxyvitamin D-3.

Regular chiropody, careful selection of footwear, and treatment of fungal infections are important. Dermabrasion may permit increased penetration of topical agents, and carbon dioxide laser treatment may be beneficial in limited keratodermas. For severe and refractory keratoderma, consider surgery. Total excision of hyperkeratotic skin followed by grafting has been successful in a number of cases. Paraneoplastic keratodermas are generally refractory to local treatment and may only respond to the removal of the underlying neoplasm.

## 19.6. Epidermolysis Bullosa

**Synonyms and related keywords:** epidermolysis bullosa, EB, epidermolysis bullosa simplex, EBS, hemidesmosomal epidermolysis bullosa, HEDB, junctional epidermolysis bullosa, JEB, dystrophic epidermolysis bullosa, recessive dystrophic epidermolysis bullosa, RDEB

**Background.**Epidermolysis bullosa (EB) is a group of inherited bullous disorders characterized by blister formation in response to mechanical trauma. Historically, EB subtypes have been classified according to skin morphology. Recent discoveries of the molecular basis of EB have resulted in the development of new diagnostic tools, including prenatal testing. Based on a better understanding of the basement membrane zone (BMZ) and the genes responsible for its components, new treatments (e.g. gene therapy) may provide solutions to the skin fragility found in patients with EB.

**Pathophysiology.**EB is classified into 3 major categories including (1) epidermolysis bullosa simplex (EBS; intraepidermal skin separation), (2) junctional epidermolysis bullosa (JEB; skin separation in lamina lucida or central BMZ), and (3) dystrophic epidermolysis bullosa (DEB; sublamina densa BMZ separation). Researchers recently have proposed a new category termed hemidesmosomal epidermolysis bullosa (HEB), which produces blistering at the hemidesmosomal level in the most superior aspect of the BMZ. EBS usually is associated with little or no extracutaneous involvement, while the more severe hemidesmosomal, junctional, and dystrophic forms of EB may produce significant multiorgan system involvement.

**Frequency.**According to the National Epidermolysis Bullosa Registry, the number of EB cases in Norway is 54.0 cases per million live births, in Japan are 7.8 cases per million live births, and in Croatia are 9.6 cases per million live births.

**Mortality/Morbidity.**Infancy is an especially difficult time for EB patients. Generalized blistering caused by any subtype may be complicated by infection, sepsis, and death. Severe forms of EB increase the mortality risk during infancy. Patients with the Herlitz or letalis form of JEB have the highest risk during infancy with an estimated mortality rate of 87% during the first year of life. In patients with EB that survive childhood, the most common cause of death is metastatic squamous cell carcinoma (SCC). This skin cancer occurs specifically in patients with recessively inherited epidermolysis bullosa (RDEB) who most commonly are aged 15-35 years. In contrast, dominantly inherited EBS and DEB and milder forms of JEB may not affect a patient's life expectancy adversely.

**Age.**Onset of EB is at birth or shortly after. The exception occurs in mild cases of EBS, which may remain undetected until adulthood or occasionally remain undiagnosed.

**History.**Important general points include age of onset; size, frequency, and location of blisters; possible inciting factors; prior diagnostic attempts; prior

therapies; and extent of pain or pruritus. In the review of systems, elicit information including alteration of growth/development and evidence of mucosal involvement, including oral, nasopharyngeal, ocular, genitourinary, GI, or respiratory symptoms. Inquire about a family history of blistering disease.

**Physical.**Perform a complete physical examination with an emphasis on inspection of all skin, as well as conjunctival, oral, and genital mucosae. Evaluate the size, location, and character of blisters. Attempt to assess the general level at which lesions split. Usually, superficial blisters manifest as crusted erosions, intraepidermal blisters are flaccid and may expand under pressure, and intralamina lucida blisters are tense and heal with atrophy but no scarring. Sublamina densa blisters heal with scarring and milia formation. Assess for involvement of nails, hair, or teeth.

**EBS** is a collection of keratin disorders characterized by intraepidermal blistering with relatively mild internal involvement. Lesions typically heal without scarring. Most commonly, these diseases are dominantly inherited, but recessively inherited cases have been reported. The more severe EBS subtypes include Koebner, Dowling-Meara, and Weber-Cockayne forms. An EBS variant associated with mottled pigmentation has been described in several families.

***Mild EBS***: Weber-Cockayne subtype is the most common form of EBS. Blisters usually are precipitated by a clearly identified traumatic event. They can be mild to severe and most frequently occur on the palms and soles. Hyperhidrosis can accompany this disorder.

***Severe EBS***: Usually, a generalized onset of blisters occurs at or shortly after birth. Hands, feet, and extremities are the most common sites of involvement. Palmoplantar hyperkeratosis and erosions are common, especially in Koebner EBS. Dowling-Meara EBS involves more oral mucosa and manifests with grouped herpetiform blisters (hence the term EBS herpetiformis).

**HEB** includes 2 rare diseases. The first arises from a disorder of the protein plectin (HD1) and is associated with muscular dystrophy. The second arises from a defect of the β6γ4 integrin receptor and is associated with pyloric atresia. Each disease shows intraepidermal blistering at the most basal aspect of the lower cell layer.

***EB with muscular dystrophy***: This condition is characterized initially by variable blistering activity, followed by onset of muscular dystrophy later in life. The degree of blistering activity does not correlate necessarily with the degree of muscular dystrophy. Some patients can present with dental abnormalities.

***EB with pyloric atresia***: this condition always is associated with pyloric atresia at birth and usually is accompanied by severe generalized blistering. In most patients, prognosis is poor despite correction of the pyloric atresia because the internal involvement is extensive. While this subtype typically is fatal during infancy, some patients with a milder case of the disease have survived into childhood.

**JEB** is a collection of diseases characterized by intralamina lucida blistering. Primary subtypes include a lethal subtype termed Herlitz or JEB letalis, a nonlethal subtype termed JEB mitis, and a generalized benign type termed generalized atrophic benign epidermolysis bullosa (GABEB).

***Lethal JEB***: The Herlitz or letalis form of JEB is characterized by generalized blistering at birth and arises from an absence or a severe defect in expression of the anchoring filament glycoprotein laminin 5. Patients with lethal forms of JEB show characteristic periorificial erosions around the mouth, eyes, and nares, often accompanied by significant hypertrophic granulation tissue. Multisystemic involvement of the corneal, conjunctival, tracheobronchial, oral, pharyngeal, esophageal, rectal, and genitourinary mucosae is present. Internal complications of the disease include a hoarse cry, cough, and other respiratory difficulties. Patients with - ***Herlitz JEB*** are at increased risk for death from sepsis or other complications secondary to the profound epithelial disadhesion, and usually, they do not survive past infancy.

***Non-lethal JEB***: Patients with JEB manifesting generalized blistering who survive infancy and clinically improve with age have JEB mitis. Usually, these patients do not present with the same type of hoarse cry or other significant respiratory symptoms as do patients with the Herlitz form. Instead, scalp, nail, and tooth abnormalities increasingly may become apparent. Periorificial erosions and hypertrophic granulation tissue can be present. Mucous membranes often are affected by erosions, resulting in strictures. Some patients with JEB mitis can present with blistering localized to the intertriginous regions.

***GABEB***: This is a relatively mild subtype characterized by generalized cutaneous blistering and presenting at birth. Blistering activity is worsened by increased ambient temperature, and blisters heal with a distinctive atrophic appearance. Extracutaneous involvement is rare, with the exception of teeth. Hypoplastic enamel formation results in significant tooth decay. Nail dystrophies and alopecia are other common clinical manifestations. Individuals with GABEB have the potential to bear children and have a typical life expectancy.

**DEB** is a group of diseases caused by defects of anchoring fibrils. Blisters heal followed by dystrophic scarring. Formation of milia (1- to 4-mm white papules) results as a consequence of damage to hair follicles.

***Dominantly inherited DEB***: The onset of disease usually is at birth or during infancy, with generalized blistering as a common presentation. With increasing age, an evolution to localized blistering is present. A common variant described by Cockayne-Touraine has an acral distribution and minimal oral or tooth involvement. Another variant described by Pasini features more extensive blistering, scar-like papules on the trunk (termed albopapuloid lesions), and involvement of the oral mucosa and teeth. Dystrophic or absent nails are common in both of these dominantly inherited DEB variants.

***RDEB***: This group of diseases ranges from mild to severe in presentation. A localized form, termed RDEB mitis, often involves acral areas and nails but shows little mucosal involvement. This subtype also demonstrates clinical manifestations similar to the dominantly inherited forms of DEB.

Severe RDEB, as described by Hallopeau-Siemens, usually shows generalized blistering at birth and subsequent extensive dystrophic scarring that is most prominent on the acral surfaces. This can produce pseudosyndactyly (mitten-hand

deformity) of the hands and feet. Flexion contractures of the extremities are increasingly common with age. Nails and teeth also are affected. Involvement of internal mucosa can result in esophageal strictures and webs, urethral and anal stenosis, phimosis, and corneal scarring. Malabsorption commonly results in a mixed anemia resulting from a lack of iron absorption, and overall malnutrition may cause failure to thrive. Patients with severe RDEB who survive to childhood are at significant risk of developing aggressive SCC in areas of chronic erosions.

**Causes.**Many stratified squamous epithelial tissues, such as the skin and oral mucosa, contain a complex BMZ. The BMZ is composed of many specialized components that combine to form anchoring complexes. At the superior aspect of the BMZ, keratin-containing intermediate filaments of the basal cell cytoskeleton insert on basal cell plasma membrane condensations termed hemidesmosomes. Anchoring filaments extend from the basal cell plasma membrane into the extracellular environment and span the lamina lucida, connecting hemidesmosomes with the lamina densa. At the most inferior aspect of the BMZ, type VII collagen-containing anchoring fibrils extend from the lamina densa into the papillary dermis, connecting the lamina densa to anchoring plaques, trapping interstitial collagen fibrils. Thus, the cutaneous BMZ connects the extensive basal cell cytoskeletal network with the abundant network of interstitial collagen fibrils in the dermis.

Keratin filaments: Keratins 5 and 14 combine to form intermediate filaments in basal keratinocytes. Keratins contain a central alpha-helical rod with several non-helical interruptions, as well as non-helical carboxyterminal and aminoterminal regions. The regions of highest conservation between the keratins are located on the ends of the keratin rod in the helix boundary motifs. Keratin intermediate filaments insert upon electron-dense structures termed hemidesmosomes.

**Complications.**SCC: arising in chronic wounds or scars of RDEB, this form of SCC is invasive and has high metastatic potential. Other EB subtypes do not show a tendency to develop SCC.

Pseudosyndactyly (mitten-hand deformity). This is a frequent complication in patients with RDEB but is rare in other subtypes. In this disorder, skin grows around the digits because of repeated blistering and dystrophic healing. Over time, the digits are encased in a mitten of skin. Therapeutic surgical approaches are available, but the rate of recurrence is high.

Mucosal complications. Patients with RDEB often have esophageal manifestations. Esophageal scarring secondary to repeated blistering and healing results in dysphagia from webbing, strictures, or stenosis. These complications are rare in patients with EBS but occur in patients with Herlitz and other nonlethal forms of JEB and dominantly inherited DEB. No cases of esophageal involvement have been reported in the generalized benign atrophic form of JEB. While patients with the Herlitz form of JEB have the greatest tendency for tracheolaryngeal involvement, RDEB may involve the tracheolaryngeal mucosa as well.

**Lab Studies.**Obtain a skin biopsy following a thorough history and physical examination. Routine histologic analysis is useful only for excluding other causes

of blistering. When EB is suspected, the best approach is to obtain 2 biopsy specimens. Analyze one specimen using electron microscopy (EM) and the other using immunofluorescent microscopy.

Evaluate anemia using CBC count with iron studies in patients with severe EB, especially RDEB.Evaluate infection using bacterial cultures from poorly healing wounds or wounds that appear infected.

**Imaging Studies.**Evaluate GI dysfunction: Esophageal strictures associated with JEB, DEB, or the pyloric atresia associated with a rare form of JEB can be visualized best by an upper GI series or endoscopy.

**Other Tests.**Evaluate nutrition using serum albumin, height and weight curves, diet diaries, and other analyses of nutrition and growth in patients with severe EB.Evaluate contractures by establishing the range of motion of limbs and digits to monitor contractures and effectiveness of physical therapy.Routine light microscopy can be used only to exclude other causes of blistering and cannot be used to make the diagnosis of EB.

**Procedures.**Electron microscopy.Obtain a biopsy specimen from a fresh blister. The best way to obtain a fresh blister is to induce it in the office by gently rotating a pencil eraser back and forth over an area of skin until epidermal separation is appreciated. Perform the biopsy at the edge of the blister, sampling both unblistered and blistered skin. Place the specimen into the appropriate holding medium (check with the laboratory beforehand) and immediately send it for transmission EM. EM biopsy holding medium usually contains glutaraldehyde.

EM is the criterion standard for determining the level of blistering. EM can provide additional information on BMZ morphology that can be helpful in making the diagnosis. For example, intermediate filament clumping indicates Dowling-Meara EBS. Rudimentary hemidesmosomes often are found in JEB subtypes. Absent or altered anchoring fibrils often occur in DEB subtypes.

Immunofluorescent microscopy can provide information on the level of the blistering.Obtain a biopsy specimen at the edge of a fresh blister for optimal results. Make arrangements with the laboratory before obtaining the specimen, and promptly send it for analysis. Zeus-holding medium is used widely for immunofluorescent microscopy.

Immunomapping with antibodies to a hemidesmosomal antigen (e.g. BP230 obtained from sera of a patient with bullous pemphigus) and an antibody to a lamina densa protein (e.g. type IV collagen) can distinguish EBS, JEB, and DEB. For example, in EBS, both antigens localize to the floor. In JEB, BP230 localizes to the roof of the blister, while type IV collagen localizes to the floor. In DEB, both antigens localize to the roof of the blister.

In addition to providing information about the level of the skin separation, immunofluorescent microscopy can be useful in providing an important clue regarding the underlying molecular defect.

DNA mutation analysis: perform mutation analysis after immunofluorescent microscopy. This is the final step in elucidating the underlying molecular defect, and in most cases, it reduces the number of genes to be screened. DNA is extracted

from blood of the patient and family members. Initial mutation screening is performed by restriction fragment-length polymorphism analysis, hotspot analysis, and finally, direct DNA sequencing.

Prenatal diagnosis: once the mutations are identified in a family, reliable prenatal diagnosis is possible. DNA for prenatal diagnosis can be obtained as a chorionic villi sample as early as the ninth week of gestation. Alternatively, amniotic fluid drawn after the eleventh week can provide the necessary DNA. Schedule the procedure in close conjunction with the diagnostic laboratory that will receive the sample.

**Medical Care.*Skin involvement*** is as follows. **Wound healing**: this process is impaired by multiple factors including foreign bodies, bacteria, nutritional deficiencies, tissue anoxia, and aging. Exogenous agents contributing to impairment of wound healing include glucocorticoids and penicillamine. Optimizing wound healing in patients with EB involves controlling all of these factors. Patients with Herlitz JEB heal slowly, which may be because of a defect in laminin 5 (a protein involved intimately in keratinocyte adhesion and migration).

**Infection.**Extensive areas of denuded skin represent loss of the stratum corneum barrier to microbial penetration. Accumulation of serum and moisture on the surface enhances the growth of bacteria. Patients with severe EB subtypes may have immunologic abnormalities, including decreased lymphocyte production or a poor nutritional status that lowers resistance to infections. *Staphylococcus aureus* and *Streptococcus pyogenes* are the usual causative organisms, but gram-negative infections with bacteria, such as *Pseudomonas aeruginosa*, also can occur. Patients also have increased susceptibility to developing sepsis. Prevention of infection is the preferred strategy. With extensive areas of crusting and denudation, a strict wound care regimen should be followed. Such a regimen entails regular whirlpool therapy followed by application of topical antibiotics. The wound should be covered with semiocclusive nonadherent dressings. Do not apply adhesive tape directly to the skin. Self-adhering gauze or tape is a better choice for keeping dressings in place.

**Tumors**. SCC often arises in chronic cutaneous lesions in patients with EB. SCC often occurs at multiple primary sites, which is especially true for patients with RDEB. In the non-EB population, cutaneous SCC arises most frequently in sun-exposed areas and primarily affects individuals with skin types I and II after the fourth decade of life. In contrast, the distribution of cutaneous SCC in patients with RDEB is different. In RDEB, SCC affects all skin types, does not show a predilection for sun-exposed sites, and peak incidence begins to increase dramatically in the second and third decades of life.Careful surveillance of non-healing areas is important.

***GI management***. The most disabling complication is esophageal lesions, which are found in Hallopeau-Siemens and inverse RDEB subtypes, Dowling-Meara, letalis EBS subtypes, and all JEB forms except localized and progressiva/neurotropica. These lesions are managed in several ways. One medical approach is to use

phenytoin and oral steroid elixirs to reduce the symptoms of dysphagia. In addition, if oral candidiasis is present, an anticandidal medication is helpful.

***Eye lesions***. Patients with EBS, particularly those with the Weber-Cockayne and Dowling-Meara subtypes, can experience recurrent blepharitis in 1 or both eyes along with bullous lesions of the conjunctivae. Patients with JEB and Hallopeau-Siemens DEB can experience corneal ulcerations, corneal scarring, obliteration of tear ducts, and eyelid lesions. Cicatricial conjunctivitis also can occur in patients with the RDEB Hallopeau-Siemens subtype. Corneal erosions are treated supportively with application of antibiotic ointment and use of cycloplegic agents to reduce ciliary spasm and provide comfort. Avoid using tape to patch the eye because of frequent blistering of the skin under the adhesive. Chronic blepharitis can result in cicatricial ectropion and exposure keratitis. Moisture chambers and ocular lubricants are used commonly for management. This disorder also has been treated with full-thickness skin grafting to the upper eyelid; however, complete correction is difficult to obtain.

***Oral care***. Good dental hygiene is essential for patients with EB, and regular visits to the dentist are recommended. If possible, a dentist familiar with EB should be consulted. Despite their best efforts, many patients with JEB and DEB develop dental caries because of enamel defects. In addition, significant oral mucosal involvement can accompany severe forms of JEB and DEB. Avoid harsh mouthwashes containing alcohol. Normal saline rinses can help gently clean the mucosal surfaces.

**Surgical Care.*GI management***: Esophageal dilation has been helpful in relieving strictures. Removal of esophageal strictures by colonic interposition has proved effective in cases of advanced disease. Gastrostomy tube insertion has been effective in providing nutrition to individuals with esophageal strictures.

***Surgical*** restoration of the hand. Mitten deformity of the hand occurs frequently in patients with the Hallopeau-Siemens DEB subtype. Repeated episodes of blistering and scarring eventually result in fusion of the web spaces. As a result, fine manipulative skills and digital prehension are lost. Surgical procedures can correct this deformity, but a high rate of recurrence is seen with mitten pseudosyndactyly. Typically, the dominant hand has earlier recurrence. Recurrence appears to be delayed by the prolonged use of splinting in the interphalangeal spaces at night.

***Surgical excision of SCC***. Invasive aggressive SCC is a particularly troubling complication of RDEB. When detected, excision of the carcinoma is indicated. Both Mohs and non-Mohs surgical approaches have been used.

***Skin equivalents***: Artificial skin grafts, such as Apligraf (Organogenesis Inc, Canton, Mass), have been useful in facilitating healing of erosions in EB and in improving the overall quality of life of patients. While the short-term effects of Apligraf have been studied carefully, the long-term effects and the persistence of grafts remain in question. Only 2 of 11 skin samples showed evidence of allograft persistence by polymerase chain reaction (a sensitive technique capable of detecting a small number of keratinocytes and/or fibroblasts) 6 weeks after grafting. Therefore, while Apligraf may represent an effective short-term therapy

for treating chronic non-healing wounds in EB, claims that Apligraf offers a long-term cure for EB remain unsubstantiated.

**Consultations.**Genetic counseling.Genetic information provided by mutation analyses on EB candidate genes provides an immediate benefit to families of patients with EB. Siblings of a patient identified as a proband with recessively inherited EB that are considering children often want to know whether they carry the mutant allele.Most importantly, prenatal diagnosis of EB in affected families currently is a genetic-based protocol, providing that the patient identified as the original proband has had mutational analysis or identification of the defective gene. Currently, fetal skin biopsies and fetoscopy, with their increased risk of pregnancy loss, can be avoided by analyzing either a chorionic villus sample as early as 8-10 weeks or amniotic fluid in the second trimester. The development of highly informative intragenic and flanking polymorphic DNA markers in EB candidate genes, together with rapid screening of genetic hotspots, make genetic screening of high-risk pregnancy a viable option.

**Diet.**Nutritional management.Increased needs: Extensive cutaneous injury is associated with marked alterations in both hemodynamic and metabolic responses, requiring increased caloric and protein intake for recovery. The burn patient has been studied extensively from both of these perspectives. Studies confirm that the development of nutritional deficiencies inhibits successful wound healing and the body's return to a normal hemodynamic and metabolic profile.

Impediments to intake and absorption: oropharyngeal and GI lesions greatly threaten the nutritional well being of patients with EB. Complications include oral blistering, abnormal esophageal motility, strictures, dysphagia, diarrhea, malabsorption, and dental problems. Nutritional assessment taking these factors into account is essential for replenishing the malnourished patient.

**Activity.**Inactivity as a result of pain and scarring can cause contractures to form. Physical therapy can be helpful in reducing limb and hand contractions and in maintaining the range of motion. EB is a genetic disease and no drugs are known to correct the underlying molecular defects. Prolonged use of steroids is contraindicated in the treatment of inherited forms of EB. Steroid-induced complications further warrant prohibiting their use. No other drugs, including phenytoin and tetracycline, have improved the blistering or epithelial disadhesion in EB significantly or consistently.

**Further Inpatient Care.**When a patient with EB is hospitalized for severe blistering, treat the blisters aggressively with wound and nutritional management. Regular whirlpool therapy can help with gentle cleansing and debridement of wounds. Whirlpool therapy is a helpful adjunct available in most hospitals and assists in the care of inpatients with EB.

**Prevention.**Prevention of trauma to the skin reduces blistering. Padding of limbs helps reduce unnecessary trauma.A soft mechanical diet helps reduce oral and esophageal erosions.

**Prognosis.**EB is a lifelong disease. Some subtypes, especially the milder EB forms, improve with age.

# XX. SEXUALLY TRANSMITTED DISEASES

## 20.1. Syphilis

**Background.***Treponema pallidum* is the microaerophilic spirochete that causes syphilis, a chronic systemic venereal disease with multiple clinical presentations (i.e. the great imitator). Syphilis is characterized by episodes of active disease (primary, secondary, tertiary stages) interrupted by periods of latency. Since the diagnosis frequently is suspected after examination of skin lesions, dermatologists are recognized as experts in the diagnosis and treatment of syphilis. Syphilis is transmitted in 2 ways, either from intimate contact with infectious lesions (most common) or blood transfusions (blood collected during early syphilis), or it is transmitted transplacentally from an infected mother to her fetus.

**Pathophysiology.**In acquired syphilis, the organism rapidly penetrates intact mucous membranes or microscopic dermal abrasions and, within a few hours, enters the lymphatics and blood to produce systemic infection. The central nervous system is invaded early in the infection; during the secondary stage, examinations demonstrate that more than 30% of patients have abnormal findings in the cerebrospinal fluid (CSF). During the first 5-10 years after infection, the disease principally involves the meninges and blood vessels, resulting in meningovascular neurosyphilis. Later, the parenchyma of the brain and spinal cord are damaged, resulting in parenchymatous neurosyphilis.

Regardless of the stage of disease and location of lesions, 2 histopathologic hallmarks of syphilis have been noted including obliterative endarteritis and plasma cell–rich mononuclear infiltrates. Endarteritis is caused by the binding of spirochetes to endothelial cells, mediated by host fibronectin molecules bound to the surface of the spirochetes. The resultant endarteritis heals with scar tissue formation.

The mononuclear infiltrates reflect a delayed-type hypersensitivity response to *T. pallidum*, and in certain individuals with tertiary syphilis, this response by sensitized T. lymphocytes and macrophages results in gummatous ulcerations and necrosis. Antigens of *T. pallidum* induce host production of treponemal antibodies and nonspecific reagin antibodies. Immunity to syphilis is incomplete. For example, host humoral and cellular immune responses may prevent the formation of a primary lesion (chancre) on subsequent infections with *T. pallidum*, but they are insufficient to clear the organism. This may be because the outer sheath of the spirochete is lacking immunogenic molecules, or it may be because of down-regulation of helper T-cells of the TH1 class.

**Frequency.**Syphilis remains prevalent in many developing countries and in some areas of North America, Asia, and Europe, especially Eastern Europe. In some regions of Siberia, as of 1999, prevalence was 1300 cases per 100,000 population.

**Mortality/Morbidity.**Although rarely seen by clinicians since the use of penicillin became widespread in the 1950s, the primary complications of syphilis in adults include neurosyphilis, cardiovascular syphilis, and gumma. Death resulting from syphilis continues to occur. One study found that of 113 recorded deaths resulting from sexually transmitted diseases, 105 were caused by syphilis, with cardiovascular and neurosyphilis accounting for the majority of these deaths. These figures have continued to increase since the emergence of the AIDS epidemic, since genital ulcer diseases (including syphilis) are cofactors for the sexual transmission of HIV. Additionally, untreated patients who are HIV seropositive have an increased risk for rapid progression to neurosyphilis and for its complications. In addition, patients with HIV are at greater risk for development or relapse of early symptomatic neurosyphilis for up to 2 years after treatment with intramuscular or intravenous penicillin.

Congenital syphilis is the most serious outcome of syphilis in women. It has been shown that a higher proportion of infants are affected if the mother has untreated secondary syphilis, compared to untreated early latent syphilis. Since *T. pallidum* does not invade the placental tissue or the fetus until the fifth month of gestation, syphilis causes late abortion, stillbirth, or death soon after delivery in more than 40% of untreated maternal infections. Neonatal mortality usually results from pulmonary hemorrhage, bacterial superinfection, or fulminant hepatitis.

**Sex.**The male-to-female ratio has increased over the past 3 years, largely due to the increased rate of disease among men who have sex with other men. In 2003, it was approximately 5:1.

**Age.**The incidence of syphilis peaks at age 15-34 years.

**History.**Primary syphilis occurs within 3 weeks of contact with an infected individual. Patients usually present with a solitary red papule that rapidly forms a painless non-bleeding ulcer or chancre. The chancre usually heals within 4-8 weeks, with or without therapy.

Secondary syphilis usually presents with a cutaneous eruption within 2-10 weeks after the primary chancre and is most florid 3-4 months after infection. The eruption may be subtle; 25% of patients may be unaware of skin changes.

Mild constitutional symptoms of malaise, headache, anorexia, nausea, aching pains in the bones, and fatigue often are present, as well as fever and neck stiffness.

A small number of patients develop acute syphilitic meningitis and present with headache, neck stiffness, facial numbness or weakness, and deafness.

The lesions of benign tertiary syphilis usually develop within 3-10 years of infection. The typical lesion is a gumma, and patient complaints usually are secondary to bone pain, which is described as a deep boring pain characteristically worse at night. Trauma may predispose a specific site to gumma involvement.CNS involvement may occur, with presenting symptoms representative of the area affected, i.e. brain involvement (headache, dizziness, mood disturbance, neck stiffness, blurred vision) and spinal cord involvement (bulbar symptoms, weakness and wasting of shoulder girdle and arm muscles, incontinence, impotence).

Some patients may present up to 20 years after infection with behavioral changes and other signs of dementia, which is indicative of neurosyphilis.

A small percentage of infants infected in utero may have a latent form of infection that becomes apparent during childhood and, in some cases, during adult life. The earliest symptom that occurs prior to age 2 years is rhinitis (snuffles), soon followed by cutaneous lesions. After age 2 years, parents may note problems with the child's hearing and language development and with vision. Facial and dental abnormalities may be noted.

**Physical.*Primary syphilis.*** The primary lesion (chancre) occurs on the penis or scrotum of 70% of men with syphilis and on the vulva, cervix, or perineum of more than 50% of women with syphilis. The primary lesion usually is a single ulcerated lesion with a surrounding red areola. The edge and base of the ulcer have a cartilaginous (button-like) consistency on palpation. The lesion is highly infectious; when abraded, it exudes a clear serum containing numerous *T. pallidum* organisms. Extragenital chancres occur most commonly above the neck, typically affecting the lips or oral cavity. The regional lymph nodes usually enlarge painlessly and are firm, discrete, and non-tender.

***Secondary syphilis.*** The protean manifestations of the secondary stage usually include localized or diffuse symmetric mucocutaneous lesions and generalized non-tender lymphadenopathy. The healing primary chancre may remain present in 15-25% of patients.Initial lesions are bilaterally symmetric, pale red to pink (in light-skinned persons) or pigmented (in dark-skinned persons), discrete, round macules that measure 5-10 mm in diameter and are distributed on the trunk and proximal extremities. After several days or weeks, red papular lesions 3-10 mm in diameter appear. These lesions often become necrotic and are distributed widely with frequent involvement of the palms and soles.Tiny papular follicular syphilids involving hair follicles may result in patchy alopecia. In addition to the classic moth-eaten alopecia, a diffuse alopecia also has been reported.In 10% of patients, highly infectious papules develop at the mucocutaneous junctions and, in moist intertriginous skin, become hypertrophic and dull pink or gray (condyloma lata).From 10-15% of patients with secondary syphilis develop superficial mucosal erosions on the palate, pharynx, larynx, glans penis, vulva, or in the anal canal and rectum. These mucous patches are circular silver-gray erosions with a red areola.

Ocular abnormalities, such as iritis, are a rare clinical finding, although anterior uveitis has been reported in 5-10% of patients with secondary syphilis.

Less common findings include periostitis, arthralgias, meningitis, nephritis, hepatitis, and ulcerative colitis.

***Tertiary syphilis.*** Gummas may be identified on the skin, in the mouth, and in the upper respiratory tract. They appear most commonly on the leg just below the knee. Gummas may be multiple or diffuse but usually are solitary lesions that range from less than 1 cm to several centimeters in diameter. Cutaneous gummas are indurated, nodular, papulosquamous or ulcerative lesions that form characteristic circles or arcs with peripheral hyperpigmentation.The most common clinical finding on cardiovascular examination is a diastolic murmur with a

tambour quality, secondary to aortic dilation with valvular insufficiency. Symptomatic neurosyphilis produces various clinical syndromes that develop in approximately 5% of patients with syphilis who remain untreated. The most common presentation of meningovascular syphilis (diffuse inflammation of the pia and arachnoid along with widespread arterial involvement) is an indolent stroke syndrome involving the middle cerebral artery. Cranial nerve palsies and pupillary abnormalities occur with basilar meningitis. Argyll Robertson pupil, which occurs almost exclusively in neurosyphilis, is a small irregular pupil that reacts normally to accommodation but not to light. Tabes dorsalis presents with signs of demyelination of the posterior columns, dorsal roots, and dorsal root ganglia (e.g. ataxic wide-based gait and foot slap, areflexia and loss of position, deep pain and temperature sensations). Deep ulcers of the feet can result from loss of pain sensation.Rare findings include iritis, with possible adhesion of the iris to the anterior lens, producing a fixed pupil (not to be confused with Argyll Robertson pupil).

***Congenital syphilis***. The manifestations of untreated congenital syphilis can be divided into those that are expressed prior to age 2 years (early) or after age 2 years (late).

**Early manifestations**

Early signs and symptoms include development of a diffuse rash, characterized by extensive sloughing of the epithelium, particularly on the palms, soles, and skin around the mouth and anus. A compilation of early clinical presentations of congenital syphilis in 9 studies involving a total of 212 infants included abnormal bone radiographs (61%), hepatomegaly (51%), splenomegaly (49%), petechiae (41%), other skin rashes (35%), anemia (34%), lymphadenopathy (32%), jaundice (30%), pseudoparalysis (28%), and snuffles (23%). A classic mucocutaneous sign is depressed linear scars radiating from the orifice of the mouth and termed rhagades (Parrot lines).

**Late manifestations**

Late signs and symptoms are rare and, if encountered, usually involve complications including interstitial keratitis, cranial nerve VIII deafness, corneal opacities, and/or recurrent arthropathy.

The clinical manifestations of untreated congenital neurosyphilis present in 25% of patients older than age 6 years and correspond to those of adult neurosyphilis.

Gummatous periostitis occurs in patients aged 5-20 years and tends to cause destructive lesions of the palate and nasal septum (saddle nose).

Dental abnormalities may be evident, such as centrally notched and widely spaced, peg-shaped, upper central incisors (Hutchinson teeth) and sixth-year molars with multiple poorly developed cusps (mulberry molars).

Peculiar bone findings include frontal bossing of Parrot and Higoumenakia sign, which is unilateral irregular enlargement of the sternoclavicular portion of the clavicle secondary to periostitis.

**Lab Studies.**In suspected acquired syphilis, perform non-treponemal serology screening using Venereal Disease Research Laboratory (VDRL), rapid plasma

reagin (RPR), or the recently developed ICE Syphilis recombinant antigen test. Then, test sera yielding a positive or equivocal reaction by the fluorescent treponemal antibody-absorption (FTA-ABS), quantitative VDRL/RPR, and microhemagglutination assay *Treponema pallidum* (MHA-TP) tests.

Dark-field microscopy is essential in evaluating moist cutaneous lesions, such as the chancre of primary syphilis or the condyloma lata of secondary syphilis. When dark-field microscopy is not available, direct immunofluorescence staining of fixed smears (direct fluorescent antibody *Treponema pallidum* [DFA-TP]) is an option. Both procedures detect the causative organism at a rate of approximately 85-92%.

For evaluation of infants with suspected congenital syphilis, the 19S immunoglobulin M FTA-ABS serology test or the Captia Syphilis-M test currently is recommended. Every pregnant woman should undergo a non-treponemal test at her first prenatal visit, and women at high risk of exposure should have a repeat test in the third trimester and again at delivery.

**Imaging Studies.**Radiologic abnormal findings commonly seen with advanced gummas of bone include periostitis, destructive osteitis, or sclerosing osteitis.

For cardiovascular complications of tertiary syphilis, linear calcification of the ascending aorta on chest films suggests asymptomatic syphilitic aortitis.Angiography may be useful to distinguish between abdominal aneurysms of syphilitic versus arteriosclerotic origin since 10% of syphilitic aneurysms occur superior to the renal arteries, while arteriosclerotic abdominal aneurysms usually are found inferior to the renal arteries.

**Other Tests.**Echocardiogram and ECG may help confirm cardiovascular syphilis.

**Procedures.**Biopsy may be necessary to differentiate gummas from coincidental granulomatous conditions.Lumbar puncture for CSF examination is indicated in the following situations: neurologic signs or symptoms, treatment failure or plans to administer treatment other than penicillin, a serum reagin titer of greater than or equal to 1:32, seropositive HIV, and other changes indicative of active syphilis (e.g. gumma, aortitis). Additionally, the only means by which the occurrence of asymptomatic neurosyphilis in latent syphilis can be excluded is via CSF examination.

**Medical Care.**Penicillin remains the mainstay of treatment and the standard by which other modes of therapy are judged (see Table 20.1). Penicillin use is the only therapy used widely for neurosyphilis, congenital syphilis, or syphilis during pregnancy. Rarely, *T. pallidum* has been found to persist following adequate penicillin therapy; however, there is no indication that the organism has acquired resistance to penicillin.In patients with allergy to penicillin, skin testing and desensitization are recommended. Make every effort to document penicillin allergy before choosing an alternative treatment because the efficacy of alternative regimens is questionable in all stages of syphilis. Many treatment failures have been reported.Tetracycline, erythromycin, and ceftriaxone have shown antitreponemal activity in clinical trials; however, they currently are recommended only as alternative treatment regimens in patients allergic to penicillin.

## Table 20.1 Treatment of Syphilis in Europe (2014 European guidelines on the management of syphilis)

| |
|---|
| **Early syphilis (Primary and Early latent, i.e. acquired ≤1 year previously)** |
| **First line therapy option** |
| Benzathine penicillin G (BPG) 2.4 million units intramuscularly (IM)<br>(one injection of 2.4 million units or 1.2 million units in each buttock) on day 1[Ib;A] |
| *Penicillin allergy or parenteral treatment refused* |
| Doxycycline 200 mg daily (either 100 mg twice daily or as a single 200 mg dose) orally for 14 days [III;B) |
| or azithromycin 2 g orally single dose [I;B] |
| **Late latent (i.e. acquired > 1 year previously or unknown duration), cardiovascular and gummatous syphilis** |
| **First line therapy option** |
| Benzathine penicillin G (BPG) 2.4 million units IM (one injection of 2.4 million units or 1.2 million units in each buttock) weekly on day 1, 8 and 15 [III;B] |
| **Penicillin allergy or parenteral treatment refused** |
| Desensitization to penicillin |
| ordoxycycline 200 mg daily (either 100 mg twice daily or as a single 200 mg dose) orally during 21-28 days [III;B] |
| ***Neurosyphilis, ocular and auricular syphilis*** |
| **First line therapy option** |
| Benzyl penicillin 18-24 million units IV daily, as 3-4 million units every 4 h during 10-14 days [III;B] |
| Second line therapy option ( if hospitalization and IV benzyl penicillin is impossible) |
| Ceftriaxone 1-2 g IV daily during 10-14 days [III;B] |
| Procaine penicillin 1.2-2.4 million units IM daily AND probenicid 500 mg four times daily, both during 10-14 days [IIb;B] |
| **Penicillin allergy** |
| Desensitization to penicillin followed by the first line regimen [III;B] |
| ***Syphilis in pregnancy*** |
| Pregnant women should be treated with the first line therapy option appropriate for the stage of syphilis and if allergic to penicillin should be desensitized. |
| ***Syphilis in HIV*** |
| Treatment should be given as for non-HIV infected patients, although there are very few data on the use of second line options |

**Consultations** are necessary depending on the specific complications and organ systems affected.

**Further Outpatient Care.**Patients with treated primary or secondary syphilis.Perform quantitative VDRL testing at 1, 3, 6, and 12 months following treatment.If the VDRL titer of 1:8 or more fails to fall at least 4 fold within 12 months or if the titer starts to rise, consider more intensive retreatment, and examine the CSF.If all clinical and serologic examinations remain satisfactory for 2 years following treatment, the patient can be reassured that cure is complete, and no further follow-up care is needed.

Patients with latent syphilis.Perform quantitative reagin testing for up to 2 years. Schedule annual follow-up visits for an indefinite period of time for patients with persistently positive serologic tests.
Patients with benign tertiary or cardiovascular syphilis: patients should be observed by the physician for the rest of their lives to monitor for complications.
Patients with neurosyphilis (both symptomatic and asymptomatic): Examine the CSF (cell count, protein, reagin titer) every 3-6 months for 3 years or until CSF findings return to normal.
**Prognosis.**For patients diagnosed with primary, or secondary syphilis (without auditory/neurologic/ocular involvement), the prognosis is good following appropriate treatment.For patients diagnosed with tertiary syphilis, overall prognosis depends on the duration and extent of disease activity, along with prior attempts to treat the disease. For example, prognosis for advanced symptomatic disease in cardiovascular syphilis is poor, unless it is treated with high doses of intravenous penicillin. In contrast, in patients with neurosyphilis complicated by optic atrophy and blindness, the ability to regain vision remains poor despite attempts with high-dose penicillin.
For patients who are pregnant and have early syphilis, it is likely that the mother will deliver a child not infected by syphilis (assuming the mother was treated appropriately).

## 20.2. Gonococcal Infections

**Background.**Gonorrhea (also called "the clap"), caused by *Neisseria gonorrhoeae,* is a public health problem and is the most common reportable infectious disease. Gonorrhea is most frequently spread during sexual contact; however, it can also be transmitted from the mother's genital tract to the newborn during birth to cause ophthalmia neonatorum and systemic neonatal infection. The incubation period is usually 2-8 days.
In women, the cervix is the most common site of infection, resulting in endocervicitis and urethritis, which can be complicated by pelvic inflammatory disease (PID). In men, infection causes anterior urethritis.
**Pathophysiology.***N. gonorrhoeae* is a gram-negative, intracellular, aerobic diplococcus. It mainly affects host columnar or cuboidal epithelium. Several factors influence the manner in which gonococci mediate their virulence and pathogenicity. Pili help in attachment of gonococci to mucosal surfaces and also contribute to resistance by preventing ingestion and killing by neutrophils. Outer membrane proteins such as opacity-associated (Opa) proteins increase adherence between gonococci (forming opaque colonies on culture media) and also increase adherence to phagocytes. Plasmid-mediated production of TEM-1–type beta-lactamase (penicillinase) also contributes to virulence.
Gonococci attach to the host mucosal cell (with the help of pili and Opa proteins) and then penetrate through and between cells into the subepithelial space. A typical host response is characterized by invasion with neutrophils, followed by epithelial

sloughing, formation of submucosal microabscesses, and purulent discharge. If left untreated, macrophages and lymphocyte infiltration replace the neutrophils. Some strains cause an asymptomatic infection, leading to an asymptomatic carrier state in persons of either sex.

**Frequency.**Disease rates are unknown for most developing countries. In much of Western Europe, rates approximate those in the United States. The incidence is substantially lower in most European countries, and indigenous gonorrhea has virtually been eliminated in Sweden. The highest incidence of gonorrhea and its complications occurs in developing countries. The median prevalence of gonorrhea in unselected populations of pregnant women has been estimated to be 10% in Africa, 5% in Latin America, and 4% in Asia.

**Mortality/Morbidity.**The major complication of gonococcal infections in women is tubal scarring and infertility. The incidence of involuntary infertility is estimated at 15% after one attack of PID and approximately 50-80% after 3 attacks. The incidence of ectopic pregnancy is increased from 7-fold to 10-fold in women with previous salpingitis, with resultant increased fetal and maternal mortality rates. Failure to diagnose PID can result in acute morbidity, including tuboovarian abscess, endometritis, or Fitz-Hugh and Curtis syndrome (perihepatitis), and the chronic sequelae noted earlier. Women may also develop gonococcal urethritis or infection of periurethral (Skene) glands or Bartholin glands.

Infertility may be more common after chlamydial PID than after gonococcal PID, presumably because the more acute inflammatory signs associated with gonorrhea prompt women to seek diagnosis and treatment sooner.

Urethral stricture caused by gonorrhea in men is less common than previously believed; some strictures in the preantibiotic era likely resulted from treatment by urethral irrigation using caustic compounds rather than from the gonorrhea itself.

**Sex.**Symptomatic disease occurs more predominantly in males than in females. An asymptomatic carrier state can occur in both sexes but is believed to occur more frequently in females than in males.Serious sequelae are much more common in women than in men. PID in women may lead to ectopic pregnancy or infertility, and women are more likely than men to develop disseminated gonococcal infection (DGI).

**Age.**In the United States, the highest rates of gonorrhea are found in young (15-30 years) unmarried persons and in groups of low educational and socioeconomic status. Infection in children is a marker for child sexual abuse.

**History.**In all patients presenting with possible STDs, the history should include past history of STDs (including HIV and viral hepatitis), known symptoms of STDs in current or past partners, type of contraception, and any history of sexual assault. In women, the history should also include the date of the last menstrual period and the details of parity, including any history of ectopic pregnancies.

***Female genitourinary tract***

The most common site of gonococcal infection in women is the endocervix (80-90%), followed by the urethra (80%), rectum (40%), and pharynx (10-20%).Major symptoms include vaginal discharge, dyspareunia, and mild lower abdominal

pain.When gonococcal cervicitis is either asymptomatic or unrecognized, the patient may progress to PID, often in proximity to a menstrual period. PID may also be asymptomatic or silent. Symptoms of PID include the following: increased vaginal discharge or purulent urethral discharge;dysuria (usually without urgency or frequency);lower abdominal pain, usually bilateral; cervical motion tenderness, adnexal tenderness,intermenstrual bleeding. Acute perihepatitis (Fitz-Hugh and Curtis syndrome) occurs primarily through direct extension of *N gonorrhoeae* or *Chlamydia trachomatis* from the fallopian tube to the liver capsule and overlying peritoneum.

***Male genitourinary tract.***In men, urethritis is the major manifestation.Initial characteristics are burning upon urination and a serous discharge. A few days later, the discharge usually becomes more profuse, purulent, and, at times, blood-tinged. Acute epididymitis can also be caused by *N gonorrhoeae,* especially in men younger than 35 years. This is usually unilateral and often occurs in conjunction with a urethral exudate.

***Male and female involvement.***Both men and women may exhibit gonococcal infection of the pharynx, rectum, and eye.Gonococcal pharyngitis is most commonly acquired during orogenital contact, with fellatio rather than cunnilingus being the more efficient form of oral sex for transmitting disease. Pharyngitis often is asymptomatic; however, it may present as exudative pharyngitis with cervical lymphadenopathy.Even though positive findings from rectal cultures for gonorrhea are noted in up to 40% of women with cervical gonorrhea (a similar percentage noted in infected homosexual men), symptoms of proctitis are unusual.Eye involvement in adults occurs by autoinoculation of gonococci into the conjunctival sac from a primary site of infection such as the genitals. The most common form of presentation is a purulent conjunctivitis, which may rapidly progress to panophthalmitis and loss of the eye unless promptly treated.

***Neonates.***In neonates, bilateral conjunctivitis (ophthalmia neonatorum) often follows vaginal delivery from an infected mother. However, transmission to the newborn can also occur in utero or in the postpartum period.The symptoms of gonococcal conjunctivitis are eye pain, redness, and a purulent discharge. Neonates may also acquire pharyngeal, respiratory, or rectal infection or DGI.The organism can cause permanent injury to the eye in a very short time; prompt recognition and treatment are essential to avoid blindness. Blindness from neonatal gonococcal infection is a serious problem in developing countries but is now uncommon in the United States and in other countries where neonatal conjunctival prophylaxis with antimicrobials is routine.

***Disseminated gonococcal infection.***DGI follows 1-2% of mucosal infections and occurs because of hematogenous dissemination of gonococci from the primary site. The symptoms vary greatly from patient to patient. By the time the symptoms of DGI appear, many patients no longer have any localized symptoms of mucosal infection.Risk factors are as follows: complement deficiency,female sex: disseminated infection may occur more frequently in women because gonorrhea in women is often asymptomatic, allowing for dissemination before symptoms occur;

menses: in menstruating females, the illness is observed shortly after the end of menstruation; pharyngeal infection and pregnancy: these may also be predisposing factors to gonococcal bacteremia;the classic presentation of DGI is arthritis dermatitis syndrome.

Joint or tendon pain is the most common presenting complaint in the early stage of infection. Many patients with DGI describe migratory polyarthralgia, especially of the knees, elbows, and more distal joints, and may also have tenosynovitis. The early tenosynovitis most commonly affects the flexor tendon sheaths of the wrist or the Achilles tendon ("lovers' heels"). The dermatitis consists of lesions varying from maculopapular to pustular, often with a hemorrhagic component. Lesions usually number 5-40, are peripherally located, and may be painful before they are visible. Fever is common, but the temperature is usually less than 39°C.

The second stage of DGI is characterized by septic arthritis, by which time the skin lesions have disappeared and blood culture results are nearly always negative. The knee is the most common site of purulent gonococcal arthritis.

Rare complications of DGI are gonococcal meningitis and endocarditis. Gonococcal meningitis may be clinically indistinguishable from meningococcal meningitis upon presentation, although the course of gonococcal meningitis is usually less rapid than that of meningococcal meningitis. Gonococcal endocarditis is more common in men than in women, with the aortic valve affected most commonly. A subacute onset of fever, chills, sweats, and malaise may indicate the presence of gonococcal endocarditis. Patients with endocarditis may develop atypical chest pain, cough, and dyspnea and may also develop the arthralgias and rash typical of DGI. Gonococcal endocarditis can cause severe valvular damage and death if not recognized and treated rapidly.

**Physical.**Patients may have the typical signs and symptoms of gonococcal diseases, especially in the genital tract. Sometimes however, patients may have no localized signs or symptoms.

***Female genitourinary tract.***Mucopurulent or purulent cervical discharge**.**Vaginal discharge or bleeding; vulvovaginitis in children.Lower abdominal tenderness with or without rebound tenderness.Adnexal tenderness (associated with ascending infection).Cervical motion tenderness (associated with ascending infection)**.** Fever.Upper right abdominal tenderness (with Fitz-Hugh and Curtis syndrome).

***Male genitourinary tract.***Mucopurulent or purulent urethral discharge.Unilateral epididymal tenderness and edema.Penile edema without other overt inflammatory signs.Urethral stricture**.**Rectal: mucopurulent or purulent discharge with or without rectal bleeding,mucopurulent exudate and inflammatory in the rectal mucosa.

Eyes: purulent conjunctivitis is usually bilateral in ophthalmia neonatorum but most often is unilateral when caused by secondary self-inoculation.

Disseminated gonococcal infection - patients with DGI may present with any of the following nonspecific findings: fever (usually < 39°C); polyarthralgia with pain; oligoarthritis.

Skin lesion are characteristically few in number and are mostly found on the distal extremities as small papulopustular lesions with an erythematous periphery.

**Causes.**Gonococcal infection usually follows mucosal inoculation during vaginal, anal, or oral sexual contact or perinatally.

Sexual contact.The risk of transmission of *N gonorrhoeae* from an infected woman to the urethra of her male partner is approximately 20% per episode of vaginal intercourse and rises to 60-80% after 4 or more exposures.In contrast, the risk of male-to-female transmission approximates 50-70% per contact, with little evidence of increased risk with more sexual exposures.Transmission through penile-rectal contact is fairly efficient. Persons who have unprotected intercourse with new partners frequently enough to sustain the infection are defined as core transmitters.

Neonatal infection may follow conjunctival inoculation during birth or direct infection through the scalp at the sites of fetal monitoring electrodes.

**Lab Studies.**Laboratory diagnosis of gonococcal infections depends on identification of *N gonorrhoeae* at an infected site.

***Isolation through culture***.This is the diagnostic standard and should be used whenever practical. A single culture on most selective media has a sensitivity of 95% or more for urethral specimens from men with symptomatic urethritis and 80-90% for endocervical infection in women. Simultaneous inoculation on selective and nonselective media may provide the highest yield. Although the urethra is commonly infected in women with gonorrhea, culturing urethral specimens does not materially increase the diagnostic yield except in women who lack cervices because of hysterectomy. Patients with possible DGI should have culture samples taken from all possible mucosal sites (i.e. pharynx, urethra, cervix, rectum) and from blood and synovial fluid. Rectal and pharyngeal specimens are inoculated onto selective medium only. When collecting specimens in males, any discharge present at the meatus can be easily recovered for examination. If no discharge is present at the meatus, urethral material must be recovered by inserting and rotating a small swab 2-3 cm into the urethra. A calcium alginate or Rayon swab on a metal shaft is recommended. When collecting specimens in women, the exocervix is first wiped of exudate. A swab is then placed into the external os and rotated for several seconds. However, take care to avoid contact with vaginal mucosa or secretions.

In patients who may have DGI, all possible mucosal sites should be cultured (e.g. pharynx, cervix, urethra, rectum), as should blood and synovial fluid (in cases of septic arthritis). Three sets of blood cultures should also be obtained. Specimens from any mucosal site should be inoculated immediately in selective media for gonorrheal organisms, such as modified Thayer-Martin, or on chocolate agar at room temperature, which should be incubated in an enriched carbon dioxide environment. The growth of typical oxidase-positive colonies that consist of gram-negative diplococci strongly suggests gonorrhea.

***Smears with Gram stain***. In men, the diagnosis of urethritis can be performed using either of 2 methods of Gram staining. The first is via a urine sample. Preferably, examine the patient at least 2 hours after micturition or before their first morning void. The patient should provide a first-morning void, and the first 10-15 mL of the urine is saved. The urine is centrifuged so that the sediment may be analyzed microscopically under high power or oil immersion. The presence of 10

or more polymorphonuclear leukocytes (PMNs) seen under high power is suggestive of urethritis. The second method is a Gram stain of urethral exudate. The presence of 4 or more PMNs per oil-immersion field is diagnostic for urethritis. In symptomatic males, Gram staining of urethral exudate has a sensitivity of 90-98% and a specificity of 95-98%. However, in asymptomatic males, the sensitivity of the Gram stain is only 60%. Therefore, culture studies are recommended if an asymptomatic gonococcal infection is suggested. The presence of typical gram-negative intracellular diplococci after Gram stain establishes a diagnosis of gonorrhea. If these organisms are not observed, the patient is said to have non-gonococcal urethritis. Results are considered equivocal if typical morphotypes not associated with neutrophils are present or if cell-associated but morphologically atypical organisms are observed. A simple Gram stain is probably the method of choice for the detection of gonorrhea in symptomatic males because it is much less expensive and much more rapid than the Gen-Probe method.

In women with positive results from cervical cultures, the Gram stain results from the endocervix are 50-60% sensitive and 82-97% specific. Also, the presence of more than 10 PMNs per high-power field on an endocervical smear is consistent with cervicitis. In women who lack cervices because of hysterectomy, use urethral culture to make the diagnosis.

No available serologic test is sufficiently sensitive and specific to merit use for screening or diagnostic purposes.

**Imaging Studies.**Ultrasound or CT scan for PID.Pelvic ultrasound or CT scan images may show thick dilated fallopian tubes or abscess formation.PID is uncommon in pregnancy. Therefore, ultrasound should be used to help rule out ectopic pregnancy whenever a pregnant patient has signs and symptoms of possible PID.In current practice, vaginal ultrasonography and CT scan help to define the cause of pelvic pain syndromes.

**Other Tests.**Various tests can be used, if available, to detect the antigen or the genome of gonococci in exudates.Fluorescein-conjugated monoclonal antibodies for direct fluorescence microscopy can be used to detect antigen.

Enzyme-linked immunoassays for the detection of gonococcal antigen with polyclonal antigonococcal antibodies can also be used.

Polymerase chain reaction tests for gonococcal DNA amplification can be used, although they are quite expensive and do not contribute much in most settings.

Ligase chain reaction tests for the presence of gonococcal DNA are also becoming available. These tests are highly specific and extremely sensitive, but they are expensive.

**Histologic Findings.**Exudate of PMNs is typical. In PID, loss of ciliated columnar epithelium from the fallopian tubes may occur. Tubes, pelvic mesentery, and ovaries may be bound together with dense fibrosis and abscess formation.

**Medical Care.**The decision to implement antimicrobial therapy should be made quickly. The choice of which regimen to use should be based on the clinical presentation. Hospitalization is recommended for initial treatment of DGI, purulent joint infections, meningitis, and endocarditis. Hospitalization is also recommended

for initial treatment of PID cases in the presence of the following factors: pregnancy, failure of outpatient treatment, tuboovarian abscess, severe symptoms (e.g. severe pain, high fever, persistent nausea and vomiting),immunodeficiency, abdominal peritonitis or perihepatitis, uncertain diagnoses, with any possibility of ectopic pregnancy or appendicitis masquerading as PID.

Uncomplicated urethritis, cervicitis, or rectal or pharyngeal infection in adults.Effective single-dose regimens currently recommended as initial therapy by the US Public Health Service for the treatment of uncomplicated gonorrhea in all patients in the United States are (1) ceftriaxone (125 mg IM), (2) cefixime (400 mg PO), (3) ciprofloxacin (500 mg PO), or ofloxacin (400 mg PO). The 125-mg intramuscular dose of ceftriaxone is fully effective. Ceftriaxone is safe and effective in pregnant women, and it probably destroys incubating syphilis. Its major drawback is the necessity for intramuscular administration. Studies suggest that ciprofloxacin at 250 mg orally is as effective as 500 mg orally, but the emergence of less-sensitive strains strongly suggests that the higher dose should be used.

Over the last decade, as fluoroquinolones have become the preferred class of antimicrobials for the treatment of gonorrhea, reports of *N. gonorrhoeae* with decreasing susceptibilities and frank resistance have surfaced. Fluoroquinolones should also be avoided, if possible, when treating pregnant women and children weighing less than 45 kg or adolescents younger than 15 years because of concerns of chondrotoxicity with this antimicrobial class. When treating gonococcal infections in pregnant women, fluoroquinolones and tetracyclines should not be used. Pregnant women should be treated with either ceftriaxone or cefixime.

Tetracyclines no longer are acceptable therapy for gonorrhea because of the prevalence of tetracycline-resistant strains. Because gonococcal infections are commonly associated with genital chlamydial infection, most authorities now recommend a 7-day course of a tetracycline (usually doxycycline) for all patients with gonorrhea as follow-up care to initial ceftriaxone therapy.

Other therapies include spectinomycin or azithromycin. Spectinomycin at 2 g intramuscularly once is effective and can be used in patients allergic to penicillin. Azithromycin at 2 g as single dose is also effective; however, its use is limited by its cost, adverse gastrointestinal effects, and lack of efficacy in pharyngeal infection.

Therapy for gonococcal arthritis.Use ceftriaxone at 1 g/d IV/IM for a total of 7 days. Oral therapy may be used initially in carefully selected compliant patients with a definite diagnosis and only mild infection. Antibiotics for oral use in this situation include cefixime (400 mg bid) or ciprofloxacin (500 mg bid) for 7 days.

Gonococcal conjunctivitis should be treated with immediate saline irrigation and intravenous ceftriaxone.

For PID therapy for outpatients, use cefoxitin at 2 g IM plus probenecid at 1g PO as a single dose or ceftriaxone at 250 mg IM followed by a 14-day oral regimen of doxycycline at 100 mg bid. Also, examining and treating all sexual partners of women with gonococcal PID is crucial.

For hospitalized patients with PID, use cefoxitin at 2 g parenterally every 6 hours or cefotetan at 2 g IV every 12 hours plus doxycycline. Alternative regimens are available. Again, examining and treating all sexual partners of women with gonococcal PID is crucial.

**Surgical Care.**Most authorities recommend removal of intrauterine devices in women with PID.Examining and treating all sexual partners of women with gonococcal PID is crucial.Septic joints should be aspirated, both to make the initial diagnosis and to remove inflammatory exudate. Open drainage is rarely indicated, except in infections of the hip in children.

**Consultations.**A gynecologist should be consulted for patients with severe PID and for any pregnant patient with an STD.A pediatrician should be consulted for any child with an STD. An ophthalmologist should be consulted for every patient with gonococcal conjunctivitis because this disease may progress rapidly and can cause permanent loss of vision.

**Further Outpatient Care.**Patients with DGI or PID who are treated in an outpatient setting must receive follow-up care within 24 hours.Early follow-up care and culture with antibiotic sensitivities are indicated for patients with unresolved or recurrent symptoms.Follow-up care for test of cure is indicated for all patients with pharyngitis treated with spectinomycin because its efficacy is less than 60%.Instruct patients with uncomplicated cases to follow up with a primary care physician or public health provider to reduce the risk of future infection.

**Prevention.**Prevention is based on education, mechanical or chemical prophylaxis, and early diagnosis and treatment. Condoms offer partial protection.All sexual contacts should be treated. Effective antibiotics taken in therapeutic doses immediately before or soon after exposure can abort an infection.Preventive measures also include attention to partner notification. Patients should be encouraged to notify their sexual partners of their exposure and encourage them to seek medical care. This is patient referral. If patients are unwilling or unable to notify their partners, then the assistance of state and local departments of public health can be enlisted. This is provider referral.All infants born to mothers with untreated gonococcal infection should be treated prophylactically with a single dose of ceftriaxone (25-50 mg/kg IV/IM, not to exceed 125 mg).All neonates should undergo prophylaxis for ophthalmia neonatorum with silver nitrate (1%) aqueous solution in both eyes once or erythromycin (0.5%) ophthalmic ointment in both eyes once.

**Complications.*Males***.Urethral stricture in adult men is less common than previously thought. Some strictures in the preantibiotic era likely resulted from treatment by urethral irrigation using caustic compounds rather than from the gonorrhea itself.Other complications, such as penile lymphangitis, periurethral abscess, acute prostatitis, seminal vesiculitis, and infection of the Tyson and Cowper glands, are now rare.

***Females.***Tubal scarring and infertility are the major complications. The incidence of involuntary infertility is estimated at 15% after one attack of PID and approximately 50-80% after 3 attacks.The incidence of ectopic pregnancy is

increased from 7-fold to 10-fold in women with previous salpingitis, with resultant increased fetal and maternal mortality rates.Failure to diagnose PID can result in acute morbidity, including tuboovarian abscess, endometritis, Fitz-Hugh and Curtis syndrome (perihepatitis), and other chronic sequelae.Infertility may be more common after chlamydial PID than after gonococcal PID, presumably because the more acute inflammatory signs associated with gonorrhea prompt women to seek diagnosis and treatment sooner. The possible compications are corneal scarring after eye infections, destruction of joint articular surfaces, destruction of cardiac valves, death from congestive heart failure related to endocarditis or from CNS complications of meningitis.

**Prognosis.**With adequate early therapy, complete cure and return to normal function are the rule.

## 20.3. Chancroid

**Synonyms and related keywords:** soft chancre, *Haemophilus ducreyi, H. ducreyi,* sexually transmitted disease, STD, genital ulcer

**Background.**Chancroid is a sexually transmitted genital ulcer disease (GUD) caused by the gram-negative bacillus *Haemophilus ducreyi*. It is characterized by the presence of painful ulcers and inflammatory inguinal adenopathy. Chancroid is often referred to as a soft chancre because the lesions are usually not indurated. In contrast, a syphilitic chancre is non-tender and indurated.

**Pathophysiology.***H. ducreyi* produces a potent cytolethal distending toxin, which is an important virulence factor in the pathogenesis of chancroid, probably contributing to both the generation and the slow healing of ulcers.

**Frequency.**In developing countries, chancroid is the cause of most GUDs and accounts for 10-30% of all sexually transmitted diseases (STDs) in Africa. The estimated worldwide incidence exceeds that of syphilis. It is endemic in Africa, Southeast Asia, Latin America, and the Caribbean.Chancroid is less common in the United States than in developing countries. However, reported cases of chancroid in the United States are on the rise in recent years, with about 4,000 cases reported annually. Outbreaks of chancroid tend to occur in poor, urban areas.

**Mortality/Morbidity.**Chancroid produces painful ulcers on the genitals, often (50%) associated with unilateral tender inguinal lymphadenitis (i.e. a bubo). Left untreated, the buboes can form fluctuant abscesses that spontaneously rupture, resulting in a non-healing ulcer.Recent studies have shown an association between chancroid and HIV. *H. ducreyi*and HIV may be cotransmitted, thereby facilitating the spread of HIV. This relationship has been especially significant in the heterosexual spread of HIV in Africa.

**Sex.**Males develop the disease most often, with a male-to-female ratio of 3-25:1. Uncircumcised men develop chancroid more often than circumcised men.Chancroid is more common in heterosexual men.Female prostitutes, either

having signs of active disease in the form of genital ulcers or being asymptomatic carriers, are an important reservoir for infection.

**Age.**Chancroid is most prevalent in sexually active and promiscuous males, with a mean patient age of 30 years.

**History.**After an incubation period of 3-7 days, the patient develops painful, erythematous papules at the site of contact. The papules become pustular and then rupture, usually forming 1-3 painful ulcers.Men usually have complaints directly related to the painful genital lesions or inguinal tenderness. Most females are asymptomatic but may present with less obvious symptoms, such as dysuria, dyspareunia, vaginal discharge, pain on defecation, or rectal bleeding. Constitutional symptoms, such as malaise and low-grade fevers, may be present.Most commonly, males report a history of recent contact with a prostitute. In addition, men who are infected are less likely to have used condoms and more likely to report a history of more than 2 sexual partners in the preceding 3 months.Intoxication with alcohol and use of cocaine have been reported more frequently in men who are infected.Men with chancroid are less likely to be circumcised. Oral sex has also been documented in the transmission of chancroid.

**Physical.**A small papule is the initial lesion at the site of infection. The papule rapidly becomes pustular and eventually ulcerates. The ulcer enlarges, develops ragged undermined borders, and is surrounded by a rim of erythema. The border of the ulcer is not indurated as in syphilis. A grayish fibrinous membrane covers the base of the ulcer. Autoinoculation results in multiple sites of infection in various stages of evolution.In men, the most common site of infection is the foreskin, but it may also occur less commonly on the shaft, the glans, or the meatus of the penis. In women, ulcers most commonly occur on the labia majora, but they may also occur on the labia minora, the thighs, the perineum, or the cervix.As many as 50% of patients have tender, fixed, inguinal lymphadenopathy, usually unilaterally, that when fluctuant is called a bubo and is highly specific for chancroid.

**Complications.**Phimosis, balanoposthitis, and rupture of buboes with fistula formation and scarring are reported complications.

**Lab Studies.**The diagnosis of chancroid based solely on the ulcer's appearance is accurate only in 30-50% of cases. In areas of high prevalence, the accuracy for clinical diagnosis of chancroid is as high as 80%; however, in areas where the disease is less common, the clinical basis for diagnosing chancroid leads to overdiagnosis. Considerable overlap exists between the major causes of GUD: herpes simplex, syphilis, chancroid, and often co-infection with 2 diseases at the same time. Co-infection with syphilis or herpes simplex virus (HSV) occurs in as many as 10% of patients. Realizing that no etiology can be found in 25-50% of all cases of GUD is important.

Gram staining may show negative coccobacilli singly, in clusters, or in a school of fish pattern.Gram staining of an ulcer specimen has low sensitivity and interpretation is hampered by polymicrobial contamination.Stains are not highly specific or sensitive, though slides with gram-negative coccobacilli in parallel rows

or in a clustered school of fish pattern have been reported to have a sensitivity of 62% and a specificity of 99% for chancroid.

Definitive diagnosis requires cultural isolation. Isolating *H. ducreyi* is difficult. Two media are available for culture. Nairobi medium consists of a biplate of (1) gonococcal agar base with 2% bovine hemoglobin, 5% fetal calf serum, and 3 mg/L of vancomycin and (2) Mueller-Hinton agar with 5% chocolatized horse blood and vancomycin. Most *H. ducreyi* organisms are sensitive to vancomycin, but some strains are inhibited by its presence. Therefore, negative cultures in the setting of high suspicion should prompt screening for vancomycin-sensitive organisms.Culture is now the accepted standard for diagnosis in most areas, but, even in an experienced laboratory, it is only 60-80% sensitive.Studies have shown the culture to be less sensitive in women than in men.Purulent material aspirated from intact buboes is almost always sterile.

PCR amplification by using primers from the 16s ribosomal RNA (rRNA) gene may provide a useful alternative to culture for the detection of *H. ducreyi*.

Immunofluorescence studies are not sensitive enough. More research is needed. A hybridoma-produced monoclonal antibody used as an immunofluorescence reagent has shown a sensitivity of 93% in detecting culture-positive chancroid.

Serologic tests for syphilis include Venereal Disease Research Laboratory (VDRL) test, rapid plasma reagin (RPR) test, and a darkfield examination.

Tests for HSV include a Tzanck smear, direct fluorescence microscopy, and culture.Consider tests for other STDs, including hepatitis B, *Chlamydia trachomatis,* gonorrhea, and HIV.

**Histologic Findings.**Histologic features from a biopsy sample of a chancroid ulcer may be sufficiently distinct to permit a presumptive diagnosis. Lesions show 3 zones. The most superficial zone is narrow and consists of neutrophils, fibrin, erythrocytes, and necrotic tissue. The second zone is wider and contains newly formed blood vessels with marked endothelial cell proliferation. The lumina of many of these vessels are occluded, leading to thrombosis. The deepest zone is composed of a dense infiltrate of plasma cells and lymphoid cells. Ducrey bacilli are seldom demonstrable on biopsy samples.

**Medical Care.**Local therapy includes topical cleansing, soaks, and measures to reduce edema. Patients with non-fluctuant buboes respond well to antibiotics, and the lesions do not need to be drained.

**Surgical Care.**Fluctuant buboes should be drained under local anesthesia. Insert a large-gauge needle into the bubo, passing through normal tissue from the side or the top of the lesion, rather than the bottom, thus avoiding continuous dependent drainage and fistula formation.Incision and drainage is an effective method for treating fluctuant buboes and may be preferable to traditional needle aspiration considering the frequency of required repeat aspirations in some studies.If circumcision is needed, it should be completed after the patient successfully completes treatment with antibiotics.

**Activity.**Patients should refrain from sexual activity until ulcers are healed. Untreated chancroid ulcers may persist for 1-3 months. Chancroid ulcers treated with the appropriate antibiotic agent resolve within 7-14 days.
**Further Outpatient Care.**Patients should receive follow-up care to ensure resolution of the disease. Clinical improvement should occur over 7 days, and healing should be complete in 2 weeks with appropriate antibiotic therapy. Lymphadenopathy may be slow to resolve and may require needle aspiration if a significant bubo is present.Because of the highly infectious nature of chancroid, routine treatment of contacts of men with chancroid is recommended even if they are asymptomatic. All sexual contacts during the 10 days prior to the development of the genital lesion should be treated.Empirical treatment of high-risk women has been shown to significantly decrease the incidence of disease.
**Prognosis.**The prognosis is excellent if chancroid is treated properly and if no co-infection with HIV is present.As many as 5% of patients have a relapse of their disease and usually respond to a repeat course of their original therapy.
**Patient Education.**The patient should be strongly advised to avoid sexual contacts while the ulcers are open because they are highly infectious and may lead to outbreaks.Patients should be advised to avoid prostitutes, to wear condoms, and to avoid having multiple partners.Cocaine and alcohol abuse should be addressed because both contribute to higher rates of the disease.

## 20.4. Lymphogranuloma Venereum

**Background.**Lymphogranuloma venereum (LGV) is a sexually transmitted chlamydial disease that should be a part of the differential diagnosis for any patient presenting with a genital ulcer and/or inguinal lymphadenopathy. Treatment involves the use of antibiotics to clear the infection and to prevent tertiary sequelae.
**Pathophysiology.***Chlamydia trachomatis,* an obligate intracellular organism, is the causative agent, and serotypes L1, L2, and L3 have been associated with infection. While other serotypes of *C trachomatis* are limited to superficial infection of mucous membranes, serotypes L1, L2, and L3 are more invasive and virulent, tending to result in systemic disease. The organism travels through the lymphatics to multiply within macrophages in regional lymph nodes. Characterization of the rate of transmission or the reservoir of *C. trachomatis* has not been defined clearly, although asymptomatic women are believed to be a source of infection.
LGV occurs in 3 stages, the first of which has an incubation period of anywhere from 3 days to 6 weeks (10-14 d average) and is characterized by a painless genital papule, which usually disappears after a few days. The onset of the second stage occurs 2-6 weeks later and often manifests as unilateral inguinal lymphadenopathy. The third stage may occur years after the initial infection and is termed genitoanorectal syndrome.

**Causes**.The causal organism is *C. trachomatis,* serotypes L1, L2, and L3; L2 is the most common.Risk factors include the following: unprotected sex, anal intercourse, sex with partners in endemic countries, multiple sex partners.
Other diagnostic considerations: causes of lymphadenopathy include sexually transmitted diseases (STDs), such as chancroid, primary and secondary syphilis, and granuloma inguinale, and non-venereal diseases, such as cat-scratch disease, infectious mononucleosis, tuberculosis, tularemia, brucellosis, bubonic plague, lymphoma, and metastatic malignancies.
**Frequency.** LGV is most common in Southeast Asia, Africa, Central America, and the Caribbean. LGV accounts for 2-10% of genital ulcer disease in India and Africa.
**Mortality/Morbidity.**Complete cure is achieved by early recognition and appropriate antibiotic treatment. Progression to the third stage of the disease can result in serious and sometimes permanent sequelae such as genital deformity, fistulas, and rectal strictures. Death is rare but may be caused by complete bowel obstruction and perforation resulting from a rectal stricture.
**Race.**As a cause of rectal strictures, LGV is found more commonly in blacks.
**Sex.**LGV is significantly more common in men than in women. Men are more likely to present with inguinal lymphadenopathy in the second stage of the disease. Women and homosexual men who engage in receptive anal intercourse are more likely to present with complications of late disease.
**Age.**Peak range is in individuals aged 15-40 years.
**History.**The primary stage is characterized by a transient non-painful lesion that usually remains unnoticed by the patient; therefore, it is rare for a patient to present with the early stage of the disease. Travel and sexual histories are important because LGV often is seen in people who have been sexually active in areas where the disease is endemic.Male patients tend to present in the second stage with painful inguinal lymphadenopathy that usually is unilateral. Constitutional symptoms, such as fever, chills, malaise, myalgias, and arthralgias, are common in this stage of the disease. Women may complain of lower abdominal or back pain because they often have involvement of deep pelvic nodes. Systemic spread occasionally can result in arthritis, pneumonitis, hepatitis, or, rarely, perihepatitis.
The tertiary stage of the disease is termed genitoanorectal syndrome. Women are more likely to present in this stage. Symptoms include fever, pain, tenesmus, pruritus, and purulent or bloody diarrhea. These symptoms are associated with proctocolitis, abscesses, and fistulas.
**Physical.*Primary stage***.The primary lesion is a small painless papule or herpetiform ulcer on the genitalia. The lesion usually heals within a few days; therefore, it is identified in only approximately 10% of patients at initial presentation. When present, lesions are found most typically on the glans penis or vaginal wall. An associated mucopurulent discharge may be present affecting the urethra in men and the cervix in women.
***Secondary stage.***The most prominent physical finding at the secondary stage is unilateral painful inguinal lymphadenopathy.Bilateral lymphadenopathy occurs in

less than one third of patients.The nodes most commonly involved are the horizontal group of inguinal nodes; however, the vertical inguinal and femoral nodes also may be affected.A characteristic physical finding, termed the groove sign, occurs in approximately one third of patients. This sign is caused by enlargement of the nodes above and below the inguinal ligament.One third of the inguinal buboes become fluctuant and rupture, while the remaining two thirds involute to form a hard non-suppurative inguinal mass.A 10:1 predominance of buboes exists in men compared to women who reach this stage of disease.Women often have primary involvement of the rectum, vagina, cervix, or posterior urethra, which drain to the deep iliac or perirectal nodes; therefore, only 20-30% have the classic finding of inguinal lymphadenopathy.

***Tertiary stage.***Physical findings at the tertiary stage include proctocolitis, perirectal abscess, fistulas, strictures, and hyperplasia of the intestinal and perirectal lymphatics (lymphorrhoids).Chronic infection can result in extensive scarring with ischemia and tissue necrosis.The end result can be esthiomene (elephantiasis of the female genitalia characterized by fibrotic labial thickening) in women or elephantiasis and deformation of the penis in men.

**Complications.**Complications usually arise from progression to the third stage of LGV. Scarring and local tissue destruction is the rule, with stricture and fistula formations and deformation of genitalia. Complete bowel obstruction from rectal stricture is possible.Systemic spread occasionally can result in arthritis, pneumonitis, hepatitis, or, rarely, perihepatitis.Rare systemic complications include pulmonary infection, cardiac involvement, aseptic meningitis, and ocular inflammatory disease.

**Lab Studies.**Diagnosis is hampered by the difficulty in culturing the organism. The best results have been obtained using aspirates from an involved inguinal lymph node and from bacterial typing of the culture after growth. Culture requires growth in cycloheximide-treated McCoy or HeLa cells, and even under these conditions, yields of only 30-50% are reported.

Serologic tests also are available and produce a strong reaction by complement fixation. Tests typically are positive within 2 weeks of disease onset and have a sensitivity of 80%. The difficulty is in separating the various serotypes of *Chlamydia* species including those involved in conjunctivitis; however, in the appropriate clinical setting, an antibody titer of 1:64 or greater or a 4-fold increase in titer is supportive of the diagnosis. Other types of chlamydial infections rarely demonstrate a titer of greater than 1:16. Antibody titers do not correlate well with clinical severity of the disease.

Other testing modalities include microimmunofluorescence and polymerase chain reaction (PCR). The usefulness of these methods is limited by availability.

**Other Tests.**Other testing may include screening for coexistence of other STDs. As with all STDs, consider concomitant infections and perform screening tests. Necessary procedures may include aspiration of buboes to speed healing and relieve discomfort.

**Histologic Findings** in the lymph nodes show focal accumulations of neutrophils in necrotic foci in the early stages. Lymphocytic hyperplasia and plasma cell infiltration follow. The classic lesion of this disease is the stellate abscess and can be identified in lymph node biopsies in secondary and, occasionally, tertiary stage disease.

**Medical Care.**Recommended treatment (see Table 20.2) is with doxycycline (100 mg PO bid) or erythromycin (500 mg qid). Continue treatment for 3 weeks, combined with aspiration of the lymph nodes if needed. Incision and drainage may result in non-healing fistula formation, which can be minimized by draining involved lymph nodes from above the inguinal ligament. Symptomatic treatment with non-steroidal anti-inflammatory drugs (NSAIDs) and local heat for pain relief may be useful adjuncts.

**Table 20.2. European guideline on the management of lynphogranulema venereum (2013)**

| **Therapy** |
|---|
| 1. First line – doxycycline 100 mg twice a day orally for 21 days (IIb;B) |
| 2.Second line – erythromycin 500 mg four times a day orally for 21 days (III, B) |
| Azithromycin in single- or multiple-dose regimen has also been proposed but evidence is lacking to currently recommend this drug (IV,C).Doxycycline is contraindicated in pregnancy and breastfeeding |
| **Adjunctive therapy** |
| 1. If fluctuant buboes appear they should be aspirated promptly through healthy adjacent skin (IV;C) |
| 2. Surgical incision of buboes is not usually recommended due to potential complications such as chronic sinus formation/ (IV;C) |
| 3. Patients with residual fibrotic lesions or fistulae do not benefit from further courses of antibiotics so surgical repair, including reconstructive genital surgery should be considered (IV, C) |

**Surgical Care.**Surgery often is necessary for repair of late complications such as fistulas and strictures.

**Consultations.**A surgery consult may be necessary for late complications or aspiration of fluctuant nodes.

**Prognosis** is excellent if LGV is treated early; however, late complications can cause significant morbidity.

## 20.5. Granuloma Inguinale (Donovanosis)

**Background.**Granuloma inguinale (GI) is primarily a sexually transmitted disease in which characteristic intracellular inclusions called Donovan bodies may be seen. It usually manifests as genital lesions, which are indolent, progressive, ulcerative, and granulomatous.

**Pathophysiology.**GI is caused by *Calymmatobacterium granulomatis,* a gram-negative pleomorphic bacillus. The mode of transmission is primarily through sexual contact, although GI may be obtained through a fecal route or by passage through an infected birth canal. It is considered to be only mildly contagious, and repeated exposure may be necessary for clinical infection to occur.
**Frequency.**GI is endemic in Western New Guinea, the Caribbean, Southern India, South Africa, Southeast Asia, Australia, and Brazil. In the US: Fewer than 100 cases are reported annually, many of which are thought to be due to foreign travel.
**Mortality/Morbidity.**Untreated, the disease will most likely not remit, and the lesions may continue to expand for years.
**Race.**The racial predilection is most likely due to socioeconomic status and living conditions rather than a racial susceptibility. The incidence is higher in blacks than in whites in the United States. The incidence is higher in natives than in Europeans in Western New Guinea. The incidence is higher in Hindus than in Moslems in India.
**Age.**The highest incidence occurs in persons aged 20-40 years.
**History.**The incubation period may range from 1 week to 3 months.
**Physical.*Morphology*.**Four varieties of skin lesions occur.
Ulcerovegetative type (most common): these lesions develop from the nodular type and consist of large, usually painless, spreading, exuberant ulcers. The ulcers have clean, friable bases with distinct, raised, rolled margins. The ulcers are typically beefy red in appearance and bleed easily. Autoinoculation is a common feature, resulting in lesions on adjacent skin.
Nodular type: soft, often pruritic, red nodules arise at the site of inoculation and eventually ulcerate and present a bright red granulating surface. (A nodule may be mistaken for a lymph node [a pseudobubo].)
Cicatricial type: dry ulcers evolve into cicatricial plaques and may be associated with lymphedema.
Hypertrophic or verrucous type (relatively rare): this proliferative reaction with formation of large vegetating masses may resemble genital warts.
Elephantiasislike swelling of the external genitalia is frequent in later-stage lesions.
***Distribution.***In men, lesions may occur on the penis, the scrotum, and/or the glans.In women, lesions may occur on the labia minora, the mons veneris, the fourchette, and/or the cervix. (Cervical involvement occurs in 10% of cases.)
***Extragenital involvement.***Lymphadenopathy does not occur due to GI, but lymph node enlargement due to secondary bacterial infection or pseudobuboes may occur. Extragenital involvement occurs in 6% of cases.Autoinoculation or direct extension may lead to involvement of the oral cavity and the gastrointestinal tract.Hematogenous dissemination to the spleen, the lungs, the liver, the bones, and the orbits may occur and occasionally results in death.
**Complications.**Once the lesions have healed, extensive fibrosis; stricture formation; and phimosis, leading to significant deformity and functional disability, may occur.Elephantiasis of the genitals may occur secondary to lymphatic destruction. Sites of healed lesions are at risk for development of squamous or

basal cell carcinomas.GI may also progress to involve extragenital sites with potentially fatal systemic spread to the viscera.

**Lab Studies.**Although isolation of *C. granulomatis* has been reported, the organism is extremely fastidious and culture is beyond the capability of most laboratories. The most effective method of establishing a diagnosis is direct visualization of the organisms within the macrophages as bipolar staining, safety pin–shaped intracytoplasmic inclusions, known as Donovan bodies. Tissue crush preparations are the most reliable method of establishing a diagnosis, although the organism can occasionally be visualized in biopsy specimens.Tissue should be obtained from the ulcer edge or base via punch biopsy, curettage, or a thin wedge. Next, the tissue is crushed between 2 glass slides, separated, and then air dried. A Wright-Giemsa or Warthin-Starry stain may be used to demonstrate the Donovan bodies.The organisms may be difficult to find in early or secondarily infected lesions or in sections stained with hematoxylin and eosin (H&E). Thin, plastic-embedded sections may allow identification of the rod-shaped encapsulated organisms within the macrophages.

**Imaging Studies.**If bony involvement is suspected, radiography or other imaging studies are indicated.

**Other Tests.**Testing for other sexually transmitted diseases is warranted because multiple coexisting infections are not uncommon.

**Histologic Findings:** The epidermis displays acanthosis at the ulcer edge, with pseudoepitheliomatous hyperplasia variably present. A dense dermal infiltrate of histiocytes and plasma cells is present, with a scattering of small neutrophilic abscesses. The macrophages are large and vacuolated, and they may demonstrate intracellular bacilli (i.e. Donovan bodies) when prepared with a Warthin-Starry or Wright-Giemsa stain.

**Medical Care.**The recommended antibiotic is either trimethoprim-sulfamethoxazole or doxycycline. Alternatives include ciprofloxacin, erythromycin, or azithromycin. The antibiotic should be given for at least a 3-week course and then continued until clearing is evident. If the ulcers do not respond within the first days of therapy, add an aminoglycoside (gentamicin 1 mg/kg IV q8h). Relapse may occur up to 18 months after treatment. Tetracycline is no longer recommended because of bacterial resistance.

Special considerations.Pregnancy is a relative contraindication for the use of sulfonamides; thus, the erythromycin regimen is advised. One should strongly consider the addition of a parenteral aminoglycoside as well.HIV-associated GI may take longer to heal, and the addition of a parenteral aminoglycoside to the regimen is also highly recommended.

**Surgical Care.**Once healed, disfiguring genital swellings may need to be surgically corrected.

**Prognosis.**Relapse may occur up to 18 months after treatment. If untreated, the lesions may continue to expand for years.

## 20.6. Chlamydial Genitourinary Infections

**Background.**Chlamydiae are small gram-negative obligate intracellular microorganisms that preferentially infect squamocolumnar epithelial cells. *Chlamydia trachomatis* is one of the 4 species (also including *Chlamydia puerorum, Chlamydia psittaci,* and *Chlamydia pneumoniae*) in the genus *Chlamydia. C. trachomatis* can be differentiated into 18 serovars (serologically variant strains) based on monoclonal antibody–based typing assays. Serovars A, B, Ba, and C are associated with trachoma (a serious eye disease that can lead to blindness), serovars D-K are associated with genital tract infections, and L1-L3 are associated with lymphogranuloma venereum ([LGV].

**Pathophysiology.**The pathophysiologic mechanisms of chlamydiae are poorly understood at best. The initial response to infected epithelial cells is a neutrophilic infiltration followed by lymphocytes, macrophages, plasma cells, and eosinophilic invasion. The release of cytokines and interferons by the infected epithelial cell initializes this inflammatory cascade.

Infection with chlamydial organisms invokes a humoral cell response, resulting in secretory immunoglobulin A (IgA) and circulatory immunoglobulin M (IgM) and immunoglobulin G (IgG) antibodies and a cellular immune response. Recent studies have implicated a 40-kd major outer membrane protein (MOMP) and a 60-kd heat-shock protein (Chsp60) in the immunopathologic response, but further studies are needed to better understand these cell-mediated immune responses.

Chlamydiae have a unique biphasic life cycle that is adaptable to both intracellular and extracellular environments. In the extracellular milieu, the so-called elementary body (EB) is found. EBs are metabolically inactive infectious particles; functionally, they are spore-type structures. Onceinside a susceptible host cell, the EB prevents phagosome-lysozyme fusion and then undergoes reorganization to form a reticulate body (RB).

The RB synthesizes its own DNA, RNA, and proteins but requires energy in the form of adenosine triphosphate (ATP) from the host cell. After a sufficient amount of RBs have formed, some transform back into EBs, exiting the cell to infect others.

**Frequency.** In 1995, the World Health Organization (WHO) estimated 89 million cases of *C trachomatis* infection worldwide. Chlamydia is the most commonly reported infectious disease in the United States - estimated at 4 million infections annually with prevalence rates of higher than 10% in sexually active adolescent females.

**Mortality/Morbidity.**Although urogenital carriage of chlamydiae often is asymptomatic, the most common manifestation of disease is local mucosal inflammation associated with a discharge, urethritis in the male, and urethritis/vaginitis/cervicitis in the female. Chlamydia is one of the leading causes of pelvic inflammatory disease (PID) and infertility in women. The risk of ectopic pregnancy in women who have had PID is 7-10 times greater than that for women without a history of PID. In 15% of women who have contracted PID, chronic

abdominal pain is a long-term manifestation that most likely is related to pelvic adhesions in the ovaries and fallopian tubes.Chlamydial infections increase the risk for acquiring HIV infection by increasing genital mucosal inflammation.Pregnant women infected with chlamydia can pass the infection on to their infants during delivery, which may develop into chlamydial pneumonia or chlamydial conjunctivitis.

**Sex.**Although the presence of asymptomatic infection with genitourinary chlamydiae can differ, acquisition is similar for both sexes.

**Age.**Age factors in chlamydial genitourinary infection relate to the age of first sexual exposure and the frequency of exposure.

**History.***C. trachomatis* is a sexually transmitted microorganism responsible for a wide spectrum of diseases that include cervicitis, salpingitis, endometritis, urethritis, epididymitis, conjunctivitis, and neonatal pneumonia. In contrast to gonorrhea infection, most men and women who are infected are asymptomatic, and, therefore, diagnosis is delayed until a positive screening result or upon discovering a symptomatic partner. Chlamydia has been isolated in approximately 40-60% of males presenting with non-gonococcal urethritis. Recent epidemiological studies indicate a high prevalence rate of asymptomatic men who act as a reservoir for chlamydial infections.

***Risk factors:*** nonwhite race**,** multiple sexual partners, age younger than 19 years, poor socioeconomic conditions**,** single marital status**,** non-barrier contraceptive use.***Neonatal risk***: conjunctivitis, neonatal pneumonia.

**Physical**

| Women | Men |
|---|---|
| - Easily endocervical bleeding<br>- Mucopurulent endocervical discharge<br>- Intermenstrual bleeding<br>- Cervical discharge<br>- Dysuria<br>- Abdominal pain | - Urethral discharge<br>- Urinary frequency and/or urgency<br>- Dysuria<br>- Scrotal pain/tenderness<br>- Perineal fullness (related to prostatitis) |

**Complications.**Reiter syndrome, a reactive arthritis secondary to an immune-mediated response has been associated (among other things) with a primary chlamydial infection.It may present as asymmetric polyarthritis, urethritis, inflammatory eye disease, mouth ulcers, circinate balanitis, and keratoderma blennorrhagica. While the etiology of Reiter syndrome may not be completely clear, 2 clear associations are observed. It usually follows an infectious episode, and 80% of affected patients are human leucocyte antigen-B27 (HLA-B27)–positive. Deeper pelvic complications in the female (PID).Potential infertility.Spread to the newborn during parturition.

**Lab Studies.**Because of the possibility of multiple sexually transmitted infections, all patients with any sexually transmitted disease (STD) should be evaluated for

chlamydial infection because chlamydial treatment is included in the Centers for Disease Control and Prevention (CDC) STD treatment regimens.

Cytologic diagnosis.This is used mainly for the diagnosis of infant inclusion conjunctivitis and in ocular trachoma by the demonstration of intracytoplasmic *C. trachomatis* inclusions in HeLa cells (i.e. continuously cultured carcinoma cell line used for tissue cultures).Cytologic diagnosis also is used to evaluate endocervical scrapings, but interpretation is difficult and sensitivity and specificity have been low.

Isolation in cell culture.*C. trachomatis* grows well in a variety of cell lines (e.g. McCoy, HeLa cells) that can be maintained in tissue culture.Incubation in tissue culture is 40-72 hours, depending on the cell type and specific biovar.Intracytoplasmic inclusions can be detected either by Giemsa stains or by immunofluorescent staining with monoclonal antibodies.Because of its high specificity (100%) and sensitivity, cell culture is the only test that should be used to establish the presence or absence of infections in cases with legal implications such as rape or sexual abuse.

Antigen detection and nucleic acid hybridization.By direct fluorescent antibody (DFA).By enzyme-linked immunosorbent assay.Detection of chlamydial ribosomal RNA (rRNA) by hybridization with a DNA probe.

***Advantage***: this is simpler and less expensive. Most studies report sensitivities greater than 70% and specificities of 97-99% in populations of men and women with a prevalence of infection of 5% or more.

***Disadvantage***: it is less sensitive when compared to tissue culture. In low-prevalence populations (i.e.<5% infected), a highly significant proportion of positive test results are false-positive results. Therefore, verification of a positive test result is desirable in certain cases. Such verification can be by culture (e.g. a second non-culture test that identifies a different chlamydial antigen or nucleic acid sequence than the first test), a blocking antibody, or competitive probe.

Detection of chlamydial genes by DNA amplification tests.Polymerase chain reaction (PCR).Ligase chain reaction (LCR).Specific chlamydial rRNA using transcription-mediated amplification.Both PCR and LCR detect *C trachomatis* in urine or self-administered vaginal swab specimens with sensitivity comparable to that with urogenital swab specimens.

Serology.Complement fixation test.All patients with LGV or psittacosis have complement-fixing antibody titers of greater than 1:16. Fifteen percent of men with urethritis and 45% of women with endocervical infection have titers 1:16 or greater.Microimmunofluorescence test.This is more sensitive than complement fixation test. Results are positive in 99% or more of women with cervicitis and in 80-90% of men with urethritis.

Antibody classes.Antichlamydia IgM is uncommon in adults with genital tract infection. The prevalence of antichlamydia IgG is high in sexually active adults, even in those who do not have an active infection, and it likely is due to past infection. A statistically significant association exists between chlamydia-specific serum IgA and active disease. The sensitivity, specificity, and predictive values are

not high enough to make any serology clinically useful in the diagnosis of active disease. Therefore, chlamydial serologies are not recommended for diagnosis of genital tract disease.The choice of the most appropriate test depends on the clinical setting, the facilities available, and the relative cost.

**Medical Care.**Patients should abstain from sexual intercourse for 7 days after single-dose therapy or until the end of a longer regimen.Patients also should refrain from sexual intercourse until all of their sex partners have been cured.Follow-up culture is not recommended after azithromycin or doxycycline therapy, but it may be considered in pregnancy after erythromycin or amoxicillin therapy. Non-culture tests should be avoided in this circumstance to avoid positive results from nonviable organisms.

**Prevention.**Individuals who are sexually active should be aware of the risk not only of genitourinary chlamydia infection but also of the whole gamut of STDs and that the best way of avoiding infection is to practice safe sex. This means using appropriate barrier protection (i.e. latex condoms).

**Prognosis.**Treatment failures with primary therapies are quite rare. Relapse may occur with alternative therapies. Reinfection is very common and is related to non-treatment of infected sexual partners or acquisition from a new partner.

## 20.7. Trichomoniasis

**Background.**Trichomoniasis is a sexually transmitted protozoal infection caused by *Trichomonas vaginalis*. Women may be asymptomatic carriers, or they may experience a range of symptoms, including a mild fulminant inflammatory disease.

**Pathophysiology.***T. vaginalis* inhabits the vaginal and urethral tissues. In women, *T. vaginalis* is isolated from the vagina, cervix, urethra, bladder, and Bartholin and Skene glands. In men, the organism is isolated from the anterior urethra, external genitalia, prostate, epididymis, and semen. Symptoms typically occur after an incubation period of 4-28 days. The protozoal pathogen causes direct damage to the epithelium, leading to microulcerations.

**Frequency.**Trichomoniasis affects approximately 180 million women worldwide. The frequency in Europe is similar to that of the United States. In Africa, the prevalence may be much higher. Trichomoniasis was present in 65% of pregnant women attending an antenatal clinic in South Africa.

**Mortality/Morbidity.**Pregnant women infected with *T. vaginalis* are 30% more likely than uninfected women to deliver preterm or to have a low birth weight infant. They are 40% more likely to deliver a preterm, low birth weight infant.Complications in men include prostatitis, epididymitis, urethral stricture disease, and infertility.*T. vaginalis* infection is highly associated with the presence of other STDs, such as gonorrhea, chlamydia, and HIV. Men with coexisting symptomatic trichomoniasis and HIV have a 6-fold increase in the concentration of HIV in their semen. Theoretically, this confers an increased risk of transmission of HIV to their sexual partners.

**Sex.**Symptomatic trichomoniasis occurs more commonly in women.Trichomoniasis infection in men is less clinically apparent; 10-50% of infected men may be asymptomatic carriers.
**Age.**Trichomoniasis is an STD; therefore, it is encountered in sexually active adolescents and adults.
**History.*Women***.Symptoms range from none in women who are asymptomatic carriers to a severe pelvic inflammatory disease.Common symptoms are yellow vaginal discharge, abnormal vaginal odor, dyspareunia, and vulvar itching.Some women may experience dysuria.
***Men.***Symptoms range from none in men who are asymptomatic carriers to urethritis complicated by prostatitis.The usual incubation period for the development of symptomatic disease is 10 days or less.Non-gonococcal urethritis is the most typical clinical syndrome in men who are symptomatic.Discharge is present in 33-50% of men who are symptomatic and varies from purulent to mucoid in character.Most symptomatic infections are intermittent and self-limiting.
**Physical.** ***Women***.Purulent or homogenous vaginal discharge and vulvar or vaginal erythema are common.Colpitis macularis, or strawberry cervix, describes a diffuse or patchy macular erythematous lesion of the cervix. This is a specific sign for trichomoniasis but is visible in only 1-2% of cases without the aid of colposcopy. With colposcopy, colpitis macularis is detected in up to 45% of cases.Lower abdominal tenderness may be present; however, this is described in fewer than 10% of patients. If this occurs, coexisting salpingitis or an intra-abdominal pathology is possible.Coexisting *Neisseria gonorrhea* infection, candidiasis, and bacterial vaginosis are common and may produce a mixed clinical picture.
***Men.***The findings on physical examination are generally unremarkable unless the infection is complicated. It may be associated with local inflammatory states, including balanitis and balanoposthitis.Physical findings of epididymitis and prostatitis also may occur.
**Lab Studies.**Laboratory studies aid in demonstration of the *T. vaginalis* organism and are used to differentiate the infection from other causes of vaginitis.Bedside laboratory studies.The vaginal pH measured on Nitrazine paper is elevated. Usually, the pH is above 5.0, and it may be as high as 6.0. Bacterial vaginosis or atrophic vaginitis also may cause elevation in the vaginal pH.Upon application of 10% potassium hydroxide to a vaginal swab sample in the potassium hydroxide amine test, a fishy odor is released, which can suggest trichomoniasis or bacterial vaginosis.
Saline microscopic examination.Obtaining a vaginal swab sample for saline wet mount evaluation is an easy, valuable, and economical tool for obtaining diagnosis.Trichomonads, which are ovoid-shaped parasites, are slightly larger than polymorphonuclear lymphocytes (PMNs) and may be identified by their ameboid mobility. Trichomonads cause an inflammatory reaction; therefore, a large number of PMNs usually are present, and this number correlates with the severity of the infection.A saline wet preparation is positive for identifying trichomonads in approximately 60% of the cases.

Papanicolaou test.Trichomonads may be viewed on Papanicolaou (Pap) test, but this test has a sensitivity of only 60-70% when compared to the use of saline microscopy.False-positive results are common with this technique.

Cultures.Incubate the cultures anaerobically.Growth is detected within 48 hours and has a sensitivity of 95%.Culture is important in establishing the diagnosis in men because the wet preparation findings are often negative.

Polymerase chain reaction (PCR) methods reportedly have high sensitivity and specificity (97% and 98%, respectively).

**Medical Care.**Systemic treatment is important to ensure a cure because trichomoniasis is an infection of multiple sites (e.g. vaginal epithelium, Skene glands, Bartholin glands, urethra).Oral metronidazole is the treatment of choice and is demonstrated in multiple studies to be superior in efficacy when compared to intravaginal treatment. Treatment failures may require a high-dose metronidazole regimen.

**Diet.**Instruct the patient to avoid alcohol while taking metronidazole because it may cause a disulfiram-like reaction.

**Further Outpatient Care.**Sexual partners of infected patients must be treated to prevent reinfection.Consider empiric treatment of other STDs that frequently coexist with trichomoniasis.Advise the patient to avoid intercourse until therapy is complete and the patientand partner are asymptomatic.

**Prevention.**Condoms and oral contraceptives may protect against transmission of trichomoniasis.

**Учебное издание**
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# КОЖНЫЕ БОЛЕЗНИ И ИНФЕКЦИИ, ПЕРЕДАВАЕМЫЕ ПОЛОВЫМ ПУТЕМ

Пособие

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Подписано в печать _____ Формат бумаги 60х84 1/16.
Бумага типографская № 2. Ризография.
Усл.печ.л. _____. Уч.-изд.л. ____. Тираж_____. Заказ_____.

Издатель и полиграфическое исполнение:
УО «Витебский государственный медицинский университет»
ЛИ № 02330/453 от 30.12.2013 г.
Пр-т Фрунзе, 27, 210023, г. Витебск