

We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

4,800

Open access books available

122,000

International authors and editors

135M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities



WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.

For more information visit www.intechopen.com



Sexually Transmitted Infections: An Overview

Nancy Malla and Kapil Goyal
Department of Parasitology, Postgraduate Institute of
Medical Education and Research, Chandigarh
India

1. Introduction

Sexually transmitted infections (STIs) are infections that are spread primarily through person-to-person sexual contact. During the past two decades, STDs have undergone a dramatic transformation. First, the change in name from venereal diseases (V.D.) to sexually transmitted diseases (STD) indicates this transformation. The term “venereal” as it relates to disease dates back to 15th century. Its root comes from the Latin *venereus* or *venus*, meaning “from sexual love or desire.” Secondly, attention is now given not only to specific sexually transmitted microbial agents, but also to clinical syndromes associated with STDs as follows:

- urethral discharge
- genital ulcers
- inguinal swellings (bubo, which is a swelling in the groin)
- scrotal swelling
- vaginal discharge
- lower abdominal pain
- neonatal eye infections (conjunctivitis of the newborn).

There are more than 30 different sexually transmissible bacteria, viruses and parasites pathogenic to man. Some of the most common are listed below:

1.1 Bacteria infections

- Neisseria gonorrhoeae*, causes gonorrhoea or gonococcal infection
- Chlamydia trachomatis*, causes chlamydial infections
- Treponema pallidum*, causes syphilis
- Haemophilus ducreyi*, causes chancroid
- Klebsiella granulomatis*, previously known as *Calymmatobacterium granulomatis* causes granuloma inguinale or donovanosis.

1.2 Viruses

- Human immunodeficiency virus, causes AIDS
- Herpes simplex virus (HSV) type 1 & 2 causes genital herpes.

- iii. Human papillomavirus (HPV)causes genital warts and certain subtypes lead to cervical cancer in women.
- iv. Hepatitis B virus, Hepatitis C virus causes hepatitis and chronic cases may lead to cancer of the liver.
- v. Molluscum contagiosum virus (member of poxvirus family), causes molluscum contagiosum virus.

1.3 Parasite

- i. *Trichomonas vaginalis*, causes vaginal trichomoniasis.

1.4 Fungal agents

- i. *Candida albicans*,causes vulvovaginitis in women; inflammation of the glans penis and foreskin in men.

1.5 Ectoparasites

- i. *Phthirus pubis*
- ii. *Sarcoptes scabiei*

Sexually transmitted diseases are divided into "traditional" or "first generation" STD (syphilis, gonorrhoea, chancroid) and "second generation" STD (Chlamydia infections and Virus infections) (Temmerman, 1992). Although many different pathogens cause STIs, some display similar or overlapping signs (what the individual or the health-care provider sees on examination) and symptoms (what the patient feels such as pain or irritation). Some of these signs and symptoms are easily recognizable and consistent, giving what is known as a syndrome that signals the presence of one or a number of pathogens. For example, a discharge from the urethra in men can be caused by gonorrhoea alone, chlamydia alone or both together. A matter of serious concern is the emergence of antimicrobial resistance to sexually transmitted microbial agents (e.g., penicillinase-producing strains of gonococci) since the late 1970s which is posing a serious barrier to patient care.

2. Significance of STI's

The true incidence of STDs is not known, because of inadequate reporting due to secrecy that surrounds these infections. The "second generation" STDs are tending to replace the first generation i.e. classical bacterial diseases (syphilis, gonorrhoea and chancroid). In many industrialized countries, the incidence of genital *C. trachomatis* infection exceeds that of gonococcal infection.

According to 2005 WHO estimates, 448 million new cases of curable STIs (syphilis, gonorrhoea, chlamydia and trichomoniasis) occur annually throughout the world in adults aged 15-49 years (WHO fact sheet 2011). This does not include HIV and other STIs which continue to adversely affect the lives of individuals and communities worldwide. In developing countries, STIs and their complications rank in the top five disease categories for which adults seek health care. Some STIs are asymptomatic and it is reported that up to 70%

of women and a significant proportion of men with gonococcal and/or chlamydial infections experience no symptoms at all. Both symptomatic and asymptomatic infections can lead to the development of serious complications, as follows.

2.1 STIs adversely affect the health of women

Untreated STIs can have critical implications for reproductive, maternal and newborn health. STIs are the main preventable cause of infertility, particularly in women. It is observed that 10 - 40% of women with untreated chlamydial infection develop symptomatic pelvic inflammatory disease. Post-infection tubal damage is responsible for 30 - 40% of cases of female infertility (Pellati et al., 2008). Furthermore, women who have had pelvic inflammatory disease are 6 - 10 times more likely to develop an ectopic (tubal) pregnancy than those who have not, and 40 - 50% of ectopic pregnancies can be attributed to previous pelvic inflammatory disease (Clark and Baranyai, 1987; Svenstrup et al., 2008). Infection with certain types of the human papillomavirus can lead to the development of genital cancers, particularly cervical cancer in women.

2.2 STIs and adverse outcomes of pregnancy

Untreated STIs are associated with congenital and perinatal infections in neonates, particularly in regions where rates of infection remain high. In pregnant women with untreated early syphilis, 25% of pregnancies result in stillbirth and 14% in neonatal death - an overall perinatal mortality of about 40%. Up to 35% of pregnancies among women with untreated gonococcal infection result in spontaneous abortions and premature deliveries, and up to 10% in perinatal deaths. In the absence of prophylaxis, 30 - 50% of infants born to mothers with untreated gonorrhoea and up to 30% of infants born to mothers with untreated chlamydial infection will develop a serious eye infection (ophthalmia neonatorum), which can lead to blindness if not treated early. Worldwide, 1000 - 4000 newborn babies become blind every year because of this condition.

2.3 STIs and HIV

The presence of untreated STIs (both those which cause ulcers or those which do not) increase the risk of both acquisition and transmission of HIV by a factor of up to 10. Prompt treatment for STIs is thus important to reduce the risk of HIV infection. Controlling STIs is important for preventing HIV infection, particularly in people with high-risk sexual behaviours.

An estimated 34 million people were living with HIV globally at the end of 2010 including 3.4 million children less than 15 (WHO, 2011). There was 2.7 million new HIV infections in 2010, including 390 000 among children less than 15. Globally, the annual number of people newly infected with HIV continues to decline, although there is stark regional variation. In sub-Saharan Africa, where most of the people newly infected with HIV live, an estimated 1.9 million people became infected in 2010. This was 16% fewer than the estimated 2.2 million people newly infected with HIV in 2001 and 27% fewer than the annual number of people newly infected between 1996 and 1998, when the incidence of HIV in sub-Saharan Africa peaked overall.

The annual number of people dying from AIDS-related causes worldwide is steadily decreasing from a peak of 2.2 million in 2005 to an estimated 1.8 million in 2010. The number of people dying from AIDS-related causes began to decline in 2005–2006 in sub-Saharan Africa, South and South-East Asia and the Caribbean and has continued subsequently. In 2010, an estimated 250 000 children less than 15 died from AIDS-related causes, 20% fewer than in 2005.

Introducing antiretroviral therapy has averted 2.5 million deaths in low- and middle-income countries globally since 1995. Sub-Saharan Africa accounts for the vast majority of the averted deaths: about 1.8 million. Providing antiretroviral prophylaxis to pregnant women living with HIV has prevented more than 350 000 children from acquiring HIV infection since 1995. Eighty-six per cent of the children who avoided infection live in sub-Saharan Africa, the region with the highest prevalence of HIV infection among women of reproductive age.

The Political Declaration on HIV/AIDS, adopted in June 2011 by the United Nations General Assembly, set ambitious targets aimed at achieving universal access and the health-related Millennium Development Goals by 2015. The WHO Global Health Sector Strategy on HIV/AIDS, 2011–2015, the UNAIDS 2011–2015 Strategy: Getting to Zero, and the UNICEF's strategic and programmatic focus on equity will help to guide national and global efforts to respond to the epidemic and move from an emergency response to a long-term, sustainable model of delivering HIV services.

2.4 STI syndromic approach

The traditional method of diagnosing STIs is by laboratory tests. However, these are often unavailable or too expensive. Since 1990 WHO has recommended a syndromic approach for the diagnosis and management of STIs in patients presenting with consistently recognized signs and symptoms of particular STIs (WHO fact sheet 2011). The syndromic approach uses flowcharts to guide diagnosis and treatment is more accurate than diagnosis based on clinical tests alone, even in experienced hands. The syndromic approach is a scientific approach and offers accessible and immediate treatment that is effective. It is also more cost-effective for some syndromes than use of laboratory tests. The pathogens causing any particular syndrome need to be determined locally and flow charts adapted accordingly. Furthermore, regular monitoring of the organisms causing each syndrome should be conducted on a regular basis to validate the treatment recommendations.

3. Genital ulcers and warts

Genital ulcers are mainly observed in the following STI's:

- i. Syphilis caused by *Treponema pallidum*
- ii. Chancroid caused by *Haemophilus ducreyi*
- iii. Genital Herpes caused by Herpes Simplex virus
- iv. Lymphogranuloma venereum (LGV) caused by *C. trachomatis*
- v. Donovanosis caused by *Calymmatobacterium granulomatosis*

Genital warts are mainly observed in the following STI's

- i. Human papilloma virus infection
- ii. Molluscum contagiosum (caused by member of poxvirus family)

3.1 General epidemiological features

Syphilis: is a sexually transmitted disease (STD) caused by the bacterium *Treponema pallidum*. It has often been called "the great imitator" because so many of the signs and symptoms are indistinguishable from those of other diseases.

According to Centers for Disease Control and Prevention (CDC fact sheet-syphilis) estimates, in the United States, health officials reported over 36,000 cases of syphilis in 2006, including 9,756 cases of primary and secondary (P&S) syphilis. In 2006, half of all P&S syphilis cases were reported from 20 counties and 2 cities; and most P&S syphilis cases occurred in persons 20 to 39 years of age. The incidence of P&S syphilis was highest in women 20 to 24 years of age and in men 35 to 39 years of age. Reported cases of congenital syphilis in newborns increased from 2005 to 2006, with 339 new cases reported in 2005 compared to 349 cases in 2006.

Between 2005 and 2006, the number of reported P&S syphilis cases increased 11.8 percent. P&S rates have increased in males each year between 2000 and 2006 from 2.6 to 5.7 and among females between 2004 and 2006. In 2006, 64% of the reported P&S syphilis cases were among men who have sex with men (MSM).

The overall syphilis rate decreased for the first time in a decade, and is down 1.6 percent since 2009 (STD Trends US 2010). However, the rate among young black men has increased dramatically over the past five years (134 percent). There is a significant increase in syphilis among young black men who have sex with men (MSM), suggesting that new infections among MSM are driving the increase in young black men. There has also been a sharp increase in HIV infections among this population (STD Trends in the United States: 2010).

Chancroid: Since 1987, reported cases of chancroid had declined steadily until 2001. Since then, the number of cases reported has fluctuated. In 2010, a total of 24 cases of chancroid were reported in the United States. Only nine states reported one or more cases of chancroid in 2010 (CDC STD surveillance 2010). Although the overall decline in reported chancroid cases most likely reflects a decline in the incidence of this disease, these data should be interpreted with caution because *Haemophilus ducreyi*, the causative organism of chancroid, is difficult to culture, and as a result, this condition may be substantially underdiagnosed.

Genital Herpes: In US, Seroprevalence decreased from 21% in 1988–1994 to 17.0% in 1999–2004 and 16.2% in 2005–2008. These data also indicate that blacks had higher seroprevalence than whites for each survey period and age group. During 2005–2008, a survey reported a diagnosis of genital herpes was 18.9% in age group of 20–49 years. Although HSV-2 seroprevalence is decreasing, most persons with HSV-2 have were not diagnosed. An increase in the number of visits for genital herpes, may indicate increased recognition of infection.

Lymphogranuloma venereum (LGV): LGV is a rare disease in industrialised countries, but is endemic in parts of Africa, Asia, South America, and the Caribbean. Its epidemiology is poorly defined, since it cannot be distinguished clinically from other causes of genital ulceration with bubo formation—for example, chancroid, and it is difficult to diagnose with confidence in the laboratory. Clinic based series of patients with genital ulcer suggest

that it is an uncommon cause of genital ulceration in Africa.(Htun et al., 1998; Behets et al., 1999) Ten per cent of patients with buboes presenting to an STD clinic in Bangkok were found to have LGV,3 and a large epidemic of LGV has been reported recently among “crack” cocaine users in the Bahamas (Bauwens et al., 2002).

Donovanosis: Even though this illness has been described for more than a century, it is frequently neglected because of its occurrence in unspecified geographical locations and with infrequent incidences. Therefore, its pathogenesis and epidemiology are not completely understood and require study (Veeranna and Raghu, 2003).

This illness is more common in Afro-Americans, in individuals with a lower socio-economic status, and among those untrained in hygiene. It is endemic in tropical and subtropical climates, such as Papua New Guinea, South Africa (provinces of KwaZulu/Natal and East Transvaal), parts of India and Indonesia, and among the aborigines of Australia. Some cases have been reported in the countries of Central America and the Caribbean, Peru (where the first cause of chronic genital ulcers in patients with immune deficiency disorder have been found), Argentina, French Guiana and Brazil. This is an illness which touches almost exclusively adults between the ages of 20 and 40 years. There are no reports of congenital infections as a result of fetal infections.(O'Farrell, 2002) However, cases have been reported in nursing and newborn babies. Cases in children are frequently associated with contact with infected adults, though not necessarily because of sexual abuse.

Human papilloma virus infection: CDC estimates in US, during 2003–2005 documented an overall high-risk HPV prevalence of 23%. Prevalence was 27% in STD clinics, 26% in family planning clinics, and 15% in primary care clinics. Prevalence by age group was 35% in women aged 14–19 years, 29% in those aged 20–29, 13% in those aged 30–39, 11% in those aged 40–49, and 6.3% in those aged 50–65 (Datta et al., 2008).

3.2 Genital ulcers

Infectious genital lesions are unique in a number of ways when compared with other infectious processes. Most are communicable and therefore are not only a clinical concern but also a public concern. Infectious genital lesion can harbour more than one pathogen at a time, making proper diagnosis and management a challenge (Dillon et al., 1997). Morphologic appearance of the ulcer or lesion itself can differ widely from one process to another and even within any single specific pathology. The unpredictable nature of lesion presentation can also make a purely clinical diagnosis unreliable. Inflammatory epithelial defects characteristic of these pathologies appear to enhance the transmission of other diseases, most importantly human immunodeficiency virus (HIV). Genital lesions may contribute substantially to the worldwide spread of this disease (Greenblatt et al., 1988). Genital ulcer disease involves a disruption of the skin and mucous membranes of the genitalia. Individuals who present with a new genital lesion and who report recent sexual activity, particularly activity with a new partner or someone with a suspected genital infection, are likely to have a sexually transmitted infection. On the other hand, certain clinical circumstances suggest non-sexually transmitted pathology, such as trauma, chemical or allergic hypersensitivity (latex allergy associated with latex condoms). A lesion that occurs proximate to sexual exposure (i.e., within hours to 1 or 2 days) may be too early to be accounted by infectious pathologies, due to variable period of incubation.

Host factors can be important historical determinants of genital lesion etiology. Patients with pre-existing psoriasis or eczema or other noninfectious dermatitides may have a genital lesion related to the underlying dermatologic pathology. Fixed drug eruption can be caused by medication such as tetracyclines or antineoplastics in a patient presenting with new genital lesion. In these cases, lesions may be characterized by pigmentation or superficial ulceration (Pandhi et al., 1984). Autoimmune diseases, such as Reiter's syndrome, Crohn's disease or Behcet's syndrome, may be associated with genital lesions (Morgan et al., 1988; Keat, 1999). The important non-infectious causes of genital ulcers have to be kept in mind in the while keeping the differential diagnosis of genital ulcers. The clinical manifestations of infectious causes of genital ulcers is described below:

3.3 Signs and symptoms

In men lesions are found on or under the prepuce, around the coronal sulcus, on the shaft of the penis, the scrotum, the perianal tissue, the inner thighs or the rectum. In the female patients, sites of involvement are equally varied. Genital lesions can appear on the mons pubis, the labia, the fourchette, anywhere in the vagina, on the cervix, the inner thighs or the perianal tissue. As a result of orogenital sex, pathogens such as HSV and syphilis can also cause orolabial lesions. Lesions of chancroid can be disseminated from the genitalia and original site of infection to distant parts, by a process of autoinoculation, although this is not common (Asin, 1952). In secondary syphilis, sometimes spirochetemia causes lesions widely dispersed from the genitalia that morphologically range from the classic papulosquamid rash of the palms and soles to the moist, raised lesions of condylomata lata (genitals) or mucous patches (orolabial area). *Neisseria gonorrhoeae*, pathogen not commonly associated with genital lesions, may disseminate and cause tender, necrotic pustules primarily on the distal extremities as part of arthritis-dermatitis syndrome (Holmes et al., 1971). Lesions associated with scabies infestation are common in the genital region as well as intertriginous areas elsewhere. Genital edema can occur after any local inflammatory process (Wright and Judson, 1979).

3.4 Pain, dysesthesias and systemic symptoms

The lesion of syphilis, lymphogranuloma venereum (LGV), scabies, and molluscum contagiosum are ordinarily painless. Granuloma inguinale (donovanosis), a genital ulcer disease seen primarily in the tropics, is caused by the bacillus *Calymmatobacterium granulomatis*. Although the lesions of this disease are often large and destructive, but it is painless. Most patients with exophytic genital warts are asymptomatic; a few may report pain or pruritus. Herpetic lesions, chancroid ulcers are typically painful. Genital lesions from immunologically mediated non-infectious causes may also be tender. Pain or other dysesthesias, including pruritus may precede the development of a recurrent disease. Pruritus is common only with ectoparasitic infestations such as scabies or lice. The pruritus associated with scabies is often described as intense and worse at night. Although pruritus may be experienced by individuals with herpes or syphilis, it is not characteristic of these conditions. Fever is occasionally seen with secondary syphilis and with primary herpes simplex infection (Brookes et al., 1992). Headache, fatigue, myalgias and malaise may also accompany these infections (Chapel, 1980). The summary of clinical features of genital ulcer disease is detailed in Table 1.

3.5 Lymphadenopathy (LAP)

Inguinal lymphadenopathy is a nonspecific finding that is characteristic of inflammatory pathology almost anywhere in the groin or either lower extremity. It often accompanies genital infection. Although the inguinal and femoral lymph nodes drain the genital region in both men and women, the inner segment of the vagina and the cervix drain into deep pelvic and perirectal lymph nodes. If these lymph are involved in inflammatory genital pathology, pelvic or rectal discomfort may be the most striking symptom.

Bilateral painless inguinal lymphadenopathy is typical in syphilis. In secondary syphilis, lymphadenopathy distant from the genital area is common. LAP associated with a herpetic genital lesion is usually bilateral and it is also tender. LGV and chancroid are characterized by expansive, tender lymph nodes called buboes. These may be unilateral or bilateral. A central area of fluctuance often develops; if left untreated. It eventually ruptures. Lymphadenitis is unusual in granuloma inguinale.

3.6 Lesion morphology

Herpes infections are characterized by vesicles that evolve into pustules and finally to shallow ulcers on an erythematous base. Multiple lesions are common which may erupt in clusters and coalesce to form a wide variety of shapes and sizes.

Syphilitic chancres are typically solitary although they may rarely occur in pairs. They are round and 1 to 2 cm in diameter, with clean margins that are indurated on palpation. The ulcer base usually lacks exudates until and unless they are super infected with other bacteria. The lesions of secondary syphilis are not chancre-like. They may start anywhere as fine, circumferential scale. In warm, moist areas such as the buttocks and genitals, unique lesions of secondary syphilis known as condylomata lata develop. These are raised, moist nodules or plaques that are teeming with treponemes. They are highly infectious.

Chancroid lesions are similar in size to syphilitic chancres but their edges are ragged and undermined. The ulcer base is necrotic with a purulent exudates. Compared with the lesions of syphilis, induration of chancroid lesions tends to be less prominent, accounting for the designation of these ulcers as "soft chancres". Despite the obvious tissue damage, adjacent inflammation is absent. Usually lesions are solitary but multiple lesions may be seen.

The lesions of granuloma inguinale start as firm subcutaneous nodules or papules that eventually ulcerate. Typically, this ulcerative process becomes hypertrophic and beefy and bleeds easily. Local tissue destruction may be extensive. Occasionally, lesions are confused with squamous cell carcinoma.

Lymphogranuloma venereum (LGV) is caused by *Chlamydia trachomatis* serovars L1, L2 and L3. At its earliest stage, LGV may cause a small papule or herpes-like ulcer. This is usually asymptomatic and resolves before recognition.

Clinically visible lesions of HPV are typically caused by viral types with low oncogenic potential (i.e. types 6 and 11). Most HPV infections are asymptomatic. Lesions may occur as flat or relatively inconspicuous papules to verrucous, pedunculated or large cauliflower like masses referred to as condylomata acuminata.

Molluscum contagiosum causes benign, wart like lesions. The etiologic agent of this condition is a member of poxvirus family.

Lesions of scabies infestation range from papules to nodules with a surrounding crust. With scratching, these lesions are often modified by excoriations or lichenification. The use of systemic or topical antimicrobial agents before clinical evaluation have a dramatic effect on lesion morphology.

3.7 Duration

Without therapy, herpes ulcers resolve within 3 weeks in cases of primary infection and recurrence resolves in 5 to 10 days. In immunocompromised patients it may persist for longer than 3 to 4 weeks. Syphilitic chancres and condylomata lata also resolve without therapy, usually between 3 and 12 weeks and usually without much scarring (Larsen et al 1995). Without therapy, the lesions of chancroid and donovanosis are slowly destructive. Scarring is typical in both these conditions. Lesions caused by HPV or molluscum contagiosum may persist unchanged for a prolonged time or they may alternate with brief periods of resolution.

3.8 Laboratory diagnosis

Laboratory tests are critical to the diagnosis and proper management of genital ulcer disease. Direct microscopic examinations e.g. dark field microscopy or direct fluorescent staining can be performed on lesion exudates or a biopsy sample, which helps in making a diagnosis. Gram staining is not usually helpful in the evaluation of genital lesions. Lesion exudates is typically laden with a variety of non-pathogenic organisms common to genitourinary and perirectal flora. Under ideal conditions, *Haemophilus ducreyi* appears as a gram negative slender rod or coccobacillus that align in a pattern referred to as "school of fish". Experienced microbiologist is required to recognize this pattern. *H. ducreyi* can be cultivated on special nutrient media using Mueller-hinton-based chocolate agar, supplemented with 1% IsoVitaleX and 3µg/mL vancomycin to inhibit the growth of other organisms (Trees and Morse, 1995). The rarity of this organism in the developed world and the expense and limited shelf life of the media make isolation of *H. ducreyi* difficult and uncommon.

Light microscopy of syphilis chancre exudates is not useful. The spirochetes are extremely thin and do not take up standard stains. Darkfield microscopy of lesion exudates from either a chancre or condylomata lata can identify spirochetes. Spirochetes appear as tightly coiled, white organisms spirally rotating against the black background of the microscopic field. To perform a proper darkfield examination, ulcers must be cleaned with gauze and saline. Exudates from the lesion is then pressed against a glass slide. The specimen should not be contaminated with too much of blood. A cover slip is then applied. Rapid examination of the specimen is essential, because desiccation reduces the viability of organisms. In vitro *T. pallidum* can not be cultured. Other diagnostic methods include direct fluorescent antibody testing and silver staining methods.

Serological testing is the most commonly used method for the diagnosis of syphilitic genital lesions. The process requires two steps: a screening test that detects serum antibodies to nontreponemal antigens (e.g., rapid plasma regain [RPR] test, Venereal Disease Research Laboratory [VDRL] test) and then a confirmatory test that detects serum antibody to specific treponemal antigens (e.g., fluorescent treponemal antibody absorbed [FTA-ABS] test, *Treponema pallidum* particle agglutination assay [TPPA]). Early after the appearance of the

syphilitic chancre, only the treponemal specific test may be reactive. Repeat testing with the nontreponemal test should be considered at some time after the ulcer has formed. In rare situations, the nontreponemal test may be falsely nonreactive in secondary syphilis due to the blocking effect of excess antibody; this is known as prozone phenomenon. Repeat testing should be performed on diluted serum samples. The cardiolipin antigens used in the detection of reaginic antibodies yield a large number of false-positive tests in many conditions other than syphilis, such as viral infections or autoimmune diseases (as a result of damage in the host's tissue). False-positive reactions have also been reported in a variety of acute and chronic diseases, such as mixed connective tissue disease, autoimmune disease, diabetes mellitus, alcoholic cirrhosis, viral infections, and pregnancy (Carlsson et al., 1991). VDRL has a prognostic significance also as it becomes non reactive after the successful treatment. Ordinarily the nontreponemal serologic test reaches its highest titer in secondary disease and declines with the onset of latency or with effective treatment (Larsen et al., 1995).

Herpes simplex virus (HSV) infected genital lesions can be identified by light microscopy using Tzanck smear. In this process, epithelial cells are scraped from an ulcer base and stained with Giemsa stain. Multinucleated giant cells and intranuclear inclusions are characteristics of HSV infections. However, both the sensitivity and specificity of the Tzanck smear are poor (Solomon et al., 1986). When available, conventional cell culture provides a relatively accurate diagnosis. Though the culture is considered to be the gold standard, it has drawback due to low sensitivity and is time consuming. Fluorescent monoclonal antibodies can be used to detect the surface antigens in smears prepared from ulcer scrapings. Molecular techniques like polymerase chain reaction targeting HSV DNA polymerase, glycoprotein D encoding regions have been successfully used to diagnose the genital herpes. Serological test, detecting IgG antibodies is not useful in diagnosing acute genital lesions.

Calymmatobacterium granulomatis, the cause of granuloma inguinale or donovanosis can be identified by staining scrapings of a lesion base with either Wright's or Giemsa's stain. Surface cells alone may not harbour the organism, so biopsy is often necessary. Clusters of blue rods, with prominent polar granules and surrounded by pink capsules are seen within infected epithelial cells and are known as Donovan bodies. Cultivation is difficult.

The diagnosis of LGV is usually based on clinical criteria. Isolation by cell culture or polymerase chain reaction of *C. Trachomatis* from bubo drainage is diagnostic. The serological test like complement fixation test and microimmunofluorescence techniques are not widely available in the diagnostic laboratories outside research centres.

The lesions of HPV are diagnosed primarily by their clinical appearance and can be assessed by cytologic methods (e.g., Papanicolaou smear) or biopsy. Infestation with ectoparasites such as *Sarcoptes scabiei* is demonstrated by identification of the organism, eggs or faeces under light microscopy. This may require the unroofing of the scabies burrow bluntly with a needle or scalpel. Nucleic acid detection is an increasingly common means of diagnosing infectious diseases. Efforts have been made to apply this technology to the diagnosis of some of the more common genital lesions. Nucleic acid detection can be performed with use of hybridization techniques, amplification techniques like PCR, TMA (transcription mediated amplification), ligase chain reaction (LCR). PCR test have been developed for *H. ducreyi* (Johnson et al., 1994), *T. pallidum* (Liu et al., 2001) and HSV (Cone et al., 1991). These technologies have also been combined in one "multiplex" platform to aid in the clinical evaluation of genital lesions. The role of such tests in current clinical practice is undefined.

	Syphilis	Chancroid	Genital herpes	Lymphogranuloma Venereum	Donovanosis
Incubation period	Avg. 21 d Range 3-90 d	2-7 d Range 1-35 d	2-7 d	Avg. 10-14 d Range 3d - 3 wk	Variable
Number of lesions	Usually single, occasionally multiple	1-3; may be multiple	Multiple; may coalesce	Usually single	Single or multiple
Border	Sharply demarcated	Erythematous and undermined	Erythematous	Variable	Rolled and elevated
Base	Red, smooth; shiny or crusty	Yellow, gray; rough	Red, smooth	Variable	Red, rough, may be friable, beefy granulations
Induration	Firm	Rare, soft	None	None	Firm
Pain	Painless; pain may occur with secondary infection	Common	Common	Variable	Rare
Lymphnodes	Unilateral to bilateral; nontender, firm	Usually unilateral; may suppurate	Usually bilateral; firm and tender	Unilateral or bilateral; firm tender, later indolent, may suppurate, groove sign present	Pseudo-adenopathy, inguinal swelling
Constitutional symptoms	Rare	Rare	Common in primary disease	Frequent	Rare

Table 1. Summary of clinical features of genital ulcer disease(Wilson and Sande).

3.9 Complications

All genital ulcers are prone to secondary bacterial infections with a variety of genital bacteria. Additionally, edema of the foreskin in uncircumcised men may produce phimosis. Without treatment, chancres of primary syphilis and lesions of genital herpes heal spontaneously. Patients with syphilis progress into the secondary stage, whereas those with genital herpes may later experience recurrence of their lesions. The ulcers of chancroid and LGV continue to grow slowly by local extension and can produce further tissue and organ damage. LGV may further lead to perianal abscesses and rectovaginal, rectovesical and anal fistulas and strictures. Lymphatic obstruction and edema may occur. Rectal LGV is associated with an increased incidence of rectal cancer. Complications of donovanosis scarring include urethral, vaginal and anal strictures and lymphedema of the external genitalia.

3.10 Treatment

Syphilis: Penicillin remains the treatment of choice for any stage of syphilis. For the penicillin allergic patient, doxycycline or tetracycline is treatment of choice.

Chancroid: A single dose of intramuscular ceftriaxone or oral azithromycin or 7 days of erythromycin are recommended first-line treatments. Alternative therapies include amoxicillin/clavulanic acid or ciprofloxacin. Fluctuant adenopathy may require needle aspiration or drainage.

Genital Herpes: Uncomplicated genital herpes heals spontaneously. Treatment is available to decrease viral shedding and shorten the duration of illness. For first episode genital herpes, oral acyclovir, valacyclovir or famciclovir is recommended for 10 days. For recurrent disease, any one of these regimens can be given for an additional 5 days. Suppressive therapy is recommended for patients with severe and frequent recurrent episodes of genital herpes.

4. Urethritis

Urethritis is the most common sexually transmitted disease (STD) syndrome recognized in men and is frequently seen in women with coinciding cervicitis. Cases can be of two types, gonococcal urethritis and nongonococcal urethritis (NGU), based on the presence or absence of *Neisseria gonorrhoeae*. The two forms are not mutually exclusive. Coinfection with *Neisseria gonorrhoeae* and *Chlamydia trachomatis* or *Ureaplasma urealyticum* occurs in 15-25% of heterosexual men with urethritis. Other agents which can cause NGU are *Trichomonas vaginalis*, Herpes simplex virus, *Mycoplasma genitalium*, *Candida spp.* NGU that occurs soon after curative therapy for gonorrhoea is called as postgonococcal urethritis (PGU).

The Centers for Disease Control and prevention estimates that NGU is 2.5-fold more prevalent than gonococcal urethritis in the United States and much of the developed world. However, gonococcal urethritis accounts for upto 80% of acute urethritis cases in certain underdeveloped regions of the world. Among people of higher socioeconomic status and college students, NGU is more common. In urban STD clinics, gonococcal urethritis is more common.

4.1 Gonococcal urethritis

N. gonorrhoeae is a gram-negative intracellular coccus that characteristically grows in pairs (diplococci). Over the last 25 years, the prevalence of penicillin and tetracycline-resistant gonococci has been increasing worldwide, requiring alternative treatment strategies. *N. gonorrhoeae* may not be limited to urethritis only but coinfection of the cervix, rectum or pharynx may also be there. Some patients may also present with disseminated infection.

4.2 Non-Gonococcal Urethritis (NGU)

Nongonococcal urethritis (NGU), which is suspected when examination findings and microscopy indicate inflammation and Gram-negative intracellular diplococci (GNID) can not be observed in stained smears and/ or culture. *C. trachomatis* is the most common etiological agent leading to NGU, in 15%–40% of cases; however, prevalence varies by age

group, with a lower burden of disease occurring among older men (Bradshaw et al., 2006). Complications of NGU among males infected with *C. trachomatis* include epididymitis and Reiter's syndrome. Documentation of chlamydial infection is essential because of the need for partner referral for evaluation and treatment. In most cases of nonchlamydial NGU, no pathogen can be detected. *M. genitalium*, which appears to be sexually transmitted, is associated with both symptoms of urethritis and urethral inflammation and accounts for 15%–25% of NGU cases in the United States (Taylor-Robinson et al., 2004; Manhart et al., 2007). *T. vaginalis*, HSV, and adenovirus also can cause NGU, but data supporting other *Mycoplasma* species and *Ureaplasma* as etiologic agents are inconsistent. Diagnostic and treatment procedures for these organisms are reserved for situations in which these infections are suspected (e.g., contact with trichomoniasis, genital lesions, or severe dysuria and meatitis, which might suggest genital herpes) or when NGU is not responsive to therapy. Enteric bacteria have been identified as an uncommon cause of NGU and might be associated with insertive anal intercourse.

4.3 Diagnosis

Clinicians should attempt to obtain objective evidence of urethral inflammation. However, if clinic-based diagnostic tools (e.g., Gram-stain microscopy) are not available, patients should be treated with drug regimens effective against both gonorrhea and chlamydia. The clinically distinguishing features of gonococcal and nongonococcal urethritis are detailed in Table 2. Urethritis can be documented on the basis of any of the following signs and/or laboratory tests:

- Mucopurulent or purulent discharge on examination.
- Gram stain of urethral secretions demonstrating ≥ 5 WBC per oil immersion field. The Gram stain is the preferred rapid diagnostic test for evaluating urethritis and is highly sensitive and specific for documenting both urethritis and the presence or absence of gonococcal infection. Gonococcal infection is established by documenting the presence of WBC containing gram-negative intracellular diplococci (GNID).
- Positive leukocyte esterase test on first-void urine or microscopic examination of first-void urine sediment demonstrating ≥ 10 WBC per high-power field.

If the urethral Gram stain is negative for gonococci, a culture should be done. *N. gonorrhoeae* is a fastidious organism requiring a selective growth medium in a carbon dioxide rich environment. Selective growth media include Thayer-Martin, Martin Lewis and New York city media. Nonculture or rapid diagnostic tests for gonococcal infection include Gonozyne, the Gen-Probe Pace 2 and the ligase chain reaction (LCR). Gonozyne is an enzyme immunoassay that can detect gonococcal antigens within urethra, cervix and urine. The gen-probe pace 2 use nonisotopic probes to detect ribosomal RNA. LCR utilizes a DNA amplification technique to detect trace amounts of organism-specific nucleic acid sequences from urethral and endo-cervical swab specimens and urine samples.

4.4 Detection of *C. trachomatis*

Cell culture is considered to be the gold standard for chlamydial testing (Gottlieb et al., 2010). It has a sensitivity of 75-80% and a specificity approaching 100%. The addition of an

enzyme immunoassay to culture increases the sensitivity to 95%. Cultures are expensive and may require 3-7 days for results. Nonculture rapid diagnostic tests, including direct fluorescence antibody (DFA) test, enzyme linked immunoassay test (EIA) and DNA probe tests, provide a more prompt diagnosis than culture with roughly an equivalent specificity (Su et al., 2011) The sensitivity is 70-90%. The Gen-Probe Pace 2 and LCR assays detect rRNA and DNA sequences, respectively of both *N. gonorrhoeae* and *C. trachomatis*. The sensitivity is higher than that of cell cultures without compromise in specificity.

If none of these criteria are present, testing for *N. gonorrhoeae* and *C. trachomatis* using nucleic acid amplification tests (NAATs) might identify additional infections. If the results demonstrate infection with either of these pathogens, the appropriate treatment should be given and sex partners referred for evaluation and treatment. If none of these criteria are present, empiric treatment of symptomatic males is recommended only for men at high risk for infection who are unlikely to return for a follow-up evaluation. Such patients should be treated with drug regimens effective against Gonorrhoea and Chlamydia. Partners of patients treated empirically should be evaluated and treated, if indicated.

4.5 Detection of other pathogens

U. urealyticum is identified by culture. Because *U. urealyticum* can be isolated in men without urethritis, a positive culture for *U. urealyticum* may not necessarily indicate the cause of urethritis. The rapid and less expensive method for the diagnosis of trichomoniasis is the direct microscopic wet mount examination of vaginal or urethral discharge. The accuracy of the exam is based on identifying motile protozoa with characteristic morphology. The wet mount exam is routinely used to evaluate women for vaginal trichomoniasis (50-70% sensitive) but is less sensitive with urethral discharge from infected men. The gold standard for diagnosing of trichomoniasis is isolating the protozoa in culture.

4.6 Treatment

Gonococcal Urethritis: Uncomplicated urethritis can be treated with Ceftriaxone 250 mg intramuscular single dose, or Cefixime 400 mg PO single dose. In 1976, penicillin-resistant gonococci were identified and found to have acquired plasmids encoding for the production of beta-lactamase. Approximately 15% of all gonococci in the United States are now penicillin resistant. In some urban areas, the incidence is as high as 60-75%. In 1985, tetracycline-resistant gonococci were identified and also found to have plasmid encoded resistance (Johnson et al., 1988). Tetracycline resistant gonococci are responsible for upto 15% of gonococcal infections along the eastern coast of the United States. *N. gonorrhoeae* with chromosomal mutations conferring penicillin and tetracycline resistance has also been identified. Because of the increasing frequency of penicillin and tetracycline resistant gonococci, the penicillins and tetracyclines are no longer recommended. Quinolone resistant gonococci have also been identified.

Intramuscular ceftriaxone cures nearly 100% of genital infections and is effective for the treatment of gonococcal infection at all sites. Ceftriaxone is also active against incubating

syphilis. Oral cefixime is nearly as active against *N. gonorrhoeae* and is less expensive. For the beta-lactam-allergic patients, oral ciprofloxacin or ofloxacin is highly effective.

Many patients who experience symptomatic relief after a single dose treatment for gonococcal urethritis develop a prompt recurrence or persistence of milder symptoms. This syndrome is called postgonococcal urethritis (PGU) and is the result of dual infection of the urethra with *N. gonorrhoeae* and organism of NGU (Gaydos et al., 2009). *N. gonorrhoeae* is eradicated by a single dose of the aforementioned cephalosporins and quinolones but the organisms responsible for NGU are often spared. PGU should be suspected if signs, symptoms or laboratory evidence of urethritis is found 4-7 days after a single-dose treatment for gonococcal urethritis. Unless chlamydial infection has been specifically ruled out through testing, all patients treated for gonococcal infections should also be treated for chlamydial infections.

Treatment of NGU: Azithromycin and doxycycline are highly effective for chlamydial urethritis; however, infections with *M. genitalium* respond better to azithromycin. Single-dose regimens have the advantage of improved compliance and directly observed treatment. To maximize compliance with recommended therapies, medications should be dispensed on-site in the clinic, and the first dose should be directly observed. To minimize transmission, men treated for NGU should be instructed to abstain from sexual intercourse for 7 days after single-dose therapy or until completion of a 7-day regimen, provided their symptoms have resolved. To minimize the risk for reinfection, men should be instructed to abstain from sexual intercourse until all of their sex partners are treated.

Tetracycline/doxycycline resistant *U. urealyticum* exist and is the basis of for treating patients with erythromycin who fail standard therapy. Treatment of urethritis due to *Trichomonas* is usually effective with a single oral dose of metronidazole.

Persons who have been diagnosed with a new STD should testing for other infections, including syphilis and HIV.

4.7 Follow-up

Patients should be instructed to return for evaluation if symptoms persist or recur after completion of therapy. Symptoms alone, without documentation of signs or laboratory evidence of urethral inflammation, are not a sufficient basis for retreatment. Providers should be alert to the possibility of chronic prostatitis/chronic pelvic pain syndrome in male patients experiencing persistent pain (perineal, penile, or pelvic), discomfort, irritative voiding symptoms, pain during or after ejaculation, or new-onset premature ejaculation lasting for >3 months.

Unless a patient's symptoms persist or therapeutic noncompliance or reinfection is suspected by the provider, a test-of-cure (i.e., repeat testing 3-4 weeks after completing therapy) is not recommended for persons with documented chlamydia or gonococcal infections who have received treatment with recommended or alternative regimens. However, because men with documented chlamydial or gonococcal infections have a high rate of reinfection within 6 months after treatment, repeat testing of all men diagnosed with chlamydia or gonorrhea is recommended 3-6 months after treatment, regardless of whether patients believe that their sex partners were treated.

Clinical finding	Gonorrhea	NGU
Onset of symptoms	Classically abrupt 75% men develop symptoms within 4 days; 80-90% men develop symptoms within 2 weeks	Less acute onset Approx. 50% men develop symptoms within 4 days
Frankly purulent urethral discharge	75%	11-33%
Mucopurulent discharge	25%	50%
Completely clear discharge	4%	10-50%
Dysuria	73-88%	53-75%

Table 2. Summary of clinical features of gonococcal and nongonococcal urethritis (Wilson and Sande).

5. Cervicitis

The microbial agents leading to cervicitis are:

- i. *N. gonorrhoeae*
- ii. *C. trachomatis*
- iii. *T. vaginalis*
- iv. Herpes simplex virus (HSV)
- v. Human papilloma virus (HPV)

Two major diagnostic signs characterize cervicitis:

1. A purulent or mucopurulent endocervical exudate visible in the endocervical canal or on an endocervical swab specimen (commonly referred to as mucopurulent cervicitis or cervicitis)
2. Sustained endocervical bleeding easily induced by gentle passage of a cotton swab through the cervical os. Either or both signs might be present. Cervicitis frequently is asymptomatic, but some women complain of an abnormal vaginal discharge and intermenstrual vaginal bleeding (e.g., after sexual intercourse). A finding of leukorrhea (>10 WBC per high-power field on microscopic examination of vaginal fluid) has been associated with chlamydial and gonococcal infection of the cervix. In the absence of inflammatory vaginitis, leukorrhea might be a sensitive indicator of cervical inflammation with a high negative predictive value. Although some specialists consider an increased number of polymorphonuclear leukocytes on endocervical Gram stain as being useful in the diagnosis of cervicitis, this criterion has not been standardized. In addition, it has a low positive-predictive value (PPV) for infection with *C. trachomatis* and *N. gonorrhoeae* and is not available in most clinical settings. Finally, although the presence of GNID on Gram stain of endocervical fluid is specific for the diagnosis of gonococcal cervical infection, it is not a sensitive indicator, because it is observed in only 50% of women with this infection.

5.1 Etiology

Mainly *C. trachomatis* or *N. gonorrhoeae* are the main etiological agents in patients suspected of cervicitis. (Hosenfeld et al., 2009) Cervicitis can also be observed in trichomoniasis and genital herpes (especially primary HSV-2 infection). However, in most cases of cervicitis, no organism is isolated, especially in women at relatively low risk for recent acquisition of these STDs (e.g., women aged >30 years). Limited data indicate that infection with *M. genitalium* and bacterial vaginosis (BV) and frequent douching might cause cervicitis. For reasons that are unclear, cervicitis can persist despite repeated courses of antimicrobial therapy, because most persistent cases of cervicitis are not caused by relapse or reinfection with *C. trachomatis* or *N. gonorrhoeae*. Other factors (e.g., persistent abnormality of vaginal flora, douching, or idiopathic inflammation in the zone of ectopy) might be involved.

5.2 Diagnosis

Cervicitis might be a sign of upper-genital-tract infection (endometritis), and thus women who seek medical treatment for a new episode of cervicitis should be assessed for signs of pelvic inflammatory disease (PID) and should be tested for *C. trachomatis* and for *N. gonorrhoeae* with the sensitive and specific tests available. Women with cervicitis also should be evaluated for the presence of Bacterial Vaginosis (BV) and trichomoniasis, for indicating specific treatment. The sensitivity of microscopy to detect *T. vaginalis* is relatively low (approximately 50%), symptomatic women with cervicitis and negative microscopy for trichomonads should be subjected to sensitive tests (i.e., culture or other FDA-cleared method). Although HSV-2 infection has been associated with cervicitis, the utility of specific testing (i.e., culture or serologic testing) for HSV-2 in this setting is unknown. Standardized diagnostic tests for *M. genitalium* are not commercially available.

Nucleic acid amplification technique (NAAT) should be used for diagnosing *C. trachomatis* and *N. gonorrhoeae* in women with cervicitis; this testing can be performed on either vaginal, cervical, or urine samples. A finding of >10 WBC in vaginal fluid, in the absence of trichomoniasis, might indicate endocervical inflammation caused specifically by *C. trachomatis* or *N. gonorrhoeae*.

5.3 Treatment

Several factors should affect the decision to provide presumptive therapy for cervicitis or to await the results of diagnostic tests. Treatment with antibiotics for *C. trachomatis* should be provided for those women at increased risk for this common STD (e.g., those aged ≤25 years, those with new or multiple sex partners, and those who engage in unprotected sex), especially if follow-up cannot be ensured and if a relatively insensitive diagnostic test is used in place of NAAT. Concurrent therapy for *N. gonorrhoeae* is indicated if the prevalence of this infection is >5% (those in younger age groups and those living in certain facilities).

Trichomoniasis and BV, if detected should also be treated. For women in whom any component of (or all) presumptive therapy is deferred, the results of sensitive tests for *C. trachomatis* and *N. gonorrhoeae* (e.g., NAATs) should determine the need for treatment subsequent to the initial evaluation.

5.4 Recommended regimens for presumptive treatment

Azithromycin 1 g orally in a single dose or doxycycline 100 mg orally twice a day for 7 days

Concurrent treatment for gonococcal infection should be considered, if prevalence of gonorrhea is high in the patient population under assessment.

5.5 Recurrent and persistent cervicitis

Women with persistent cervicitis should be reevaluated for possible reexposure to an STD. If relapse and/or reinfection with a specific STD has been excluded, BV is not present, and sex partners have been evaluated and treated, management options for persistent cervicitis are undefined; in addition, the utility of repeated or prolonged administration of antibiotic therapy for persistent symptomatic cervicitis remains unknown. Women who receive such therapy should be followed up post-treatment so that a determination can be made regarding whether cervicitis has resolved. Research is needed on the etiology of persistent cervicitis including the potential role of *M. genitalium*. In women with persistent symptoms that are clearly attributable to cervicitis, referral to a gynecologic specialist can be considered.

5.6 Follow up

Follow-up should be conducted as recommended for the infections for which a woman is treated. If symptoms persist, women should be instructed to return for re-evaluation because women with documented chlamydial or gonococcal infections have a high rate of reinfection within 6 months after treatment. Therefore, repeat testing of all women for Chlamydia and/ or Gonococcus is recommended 3-6 months after treatment, regardless of whether their sex partners were treated.

5.7 Management of sex partners

Management of sex partners of women treated for cervicitis should be appropriate for the identified or suspected STD. Partners should be notified and examined if Chlamydia, Gonococcus, or *T. vaginalis* was identified or suspected in the index patient; these partners should then be treated for the STDs for which the index patient received treatment. To avoid reinfection, patients and their sex partners should abstain from sexual intercourse until therapy is completed (i.e., 7 days after a single-dose regimen or after completion of a 7-day regimen). Expedited partner treatment and patient referral are alternative approaches to treating male partners of women that have Chlamydia or gonococcal infections.

6. Sexually transmitted infections characterized by vaginal discharge

Most women will have a vaginal infection, characterized by discharge, itching, or odor, during their lifetime. Obtaining a medical history alone has been shown to be insufficient for accurate diagnosis of vaginitis and can lead to the inappropriate administration of medication. Therefore, a careful history, examination, and laboratory testing to determine the etiology of vaginal complaints are warranted. Information on sexual behaviors and

practices, gender of sex partners, menstrual history, vaginal hygiene practices (such as douching), and other medications should be elicited. The three diseases most frequently associated with vaginal discharge are bacterial vaginosis (BV caused by the replacement of the vaginal flora by an overgrowth of anaerobic bacteria including *Prevotella* sp., *Mobiluncus* sp., *G. vaginalis*, *Ureaplasma*, *Mycoplasma*, and numerous fastidious or uncultivated anaerobes), trichomoniasis (caused by *T. vaginalis*), and candidiasis (usually caused by *Candida albicans*). The summary of clinical features of vaginitis is depicted in Table 3. Cervicitis also can sometimes cause a vaginal discharge. Although vulvovaginal candidiasis (VVC) usually is not transmitted sexually, it is included in this chapter because it is frequently diagnosed in women who have vaginal complaints or who are being evaluated for STDs.

Various diagnostic methods are available to identify the etiology of an abnormal vaginal discharge (Khan et al., 2009). Clinical laboratory testing can identify the cause of vaginitis in most women. The cause of vaginal symptoms might be determined by pH, a potassium hydroxide (KOH) test, and microscopic examination of fresh samples of the discharge on bed side examination. The pH of the vaginal secretions can be determined by narrow-range pH paper; an elevated pH (i.e., >4.5) is common with BV or trichomoniasis. Because pH testing is not highly specific, discharge should be further examined microscopically by first diluting one sample in one to two drops of 0.9% normal saline solution on one slide and a second sample in 10% KOH solution. Cover slips are then placed on the slides, and they are examined under a microscope at low and high power. Samples that emit an amine odor immediately upon application of KOH suggest BV or trichomoniasis infection.

The saline-solution specimen might yield motile *T. vaginalis*, or clue cells (i.e., epithelial cells with borders obscured by small bacteria), which are characteristic of BV, whereas the presence of WBCs without evidence of trichomonads or yeast is suggestive of cervicitis. The KOH specimen typically is used to identify the yeast or pseudohyphae of *Candida* species. However, the absence of trichomonads or pseudohyphae in KOH samples does not rule out these infections, because the sensitivity of microscopy is approximately 50% compared with NAAT or culture.

In settings where pH paper, KOH, and microscopy are not available, alternative commercially available point-of-care tests or clinical laboratory testing can be used to diagnose vaginitis. The presence of objective signs of vulvar inflammation in the absence of vaginal pathogens after laboratory testing, along with a minimal amount of discharge, suggests the possibility of mechanical, chemical, allergic, or other noninfectious irritation of the vulva.

6.1 Bacterial Vaginosis (BV)

BV is a polymicrobial clinical syndrome resulting from replacement of the normal hydrogen peroxide producing *Lactobacillus* sp. in the vagina with high concentrations of anaerobic bacteria (e.g., *Prevotella* sp. and *Mobiluncus* sp.), *G. vaginalis*, *Ureaplasma*, *Mycoplasma*, and numerous fastidious or uncultivated anaerobes (Livengood, 2009). Some women experience transient vaginal microbial changes, whereas others experience them for a longer intervals of time. Among women attending hospital for routine checkup, BV is the most prevalent cause of vaginal discharge or malodour. BV is associated with having multiple male or

female partners, a new sex partner, douching, lack of condom use, and lack of vaginal lactobacilli; women who have never been sexually active can also be affected. The cause of the microbial alteration that characterizes BV is not fully understood, nor is whether BV results from acquisition of a sexually transmitted pathogen. Nonetheless, women with BV are at increased risk for the acquisition of some STDs (e.g., HIV, *N. gonorrhoeae*, *C. trachomatis*, and HSV), complications after gynecologic surgery, complications of pregnancy, and recurrence of BV. Treatment of male sex partners has not been beneficial in preventing the recurrence of BV.

6.2 Diagnosis

BV can be diagnosed by the use of clinical criteria (i.e., Amsel's Diagnostic Criteria) or Gram stain. A Gram stain, considered the gold standard laboratory method for diagnosing BV, is used to determine the relative concentration of lactobacilli (i.e., long Gram-positive rods), Gram-negative and Gram-variable rods and cocci (i.e., *G. vaginalis*, *Prevotella*, *Porphyromonas*, and *peptostreptococci*), and curved Gram-negative rods (i.e., *Mobiluncus*) characteristic of BV (Khan et al., 2009). If a Gram stain is not available, clinical criteria can be used and require three of the following symptoms or signs:

- homogeneous, thin, white discharge that smoothly coats the vaginal walls;
- presence of clue cells on microscopic examination;
- pH of vaginal fluid >4.5;
- a fishy odor of vaginal discharge before or after addition of 10% KOH (i.e., the whiff test).

Detection of three of these criteria has been correlated with results by Gram stain. Other tests, including a DNA probe-based test for high concentrations of *G. vaginalis* (Affirm VP III, Becton Dickinson, Sparks, Maryland), a proline-aminopeptidase test card (Pip Activity TestCard, Quidel, San Diego, California), and the OSOM BVBlue test have acceptable performance characteristics compared with Gram stain. Although a card test is available for the detection of elevated pH and trimethylamine, it has low sensitivity and specificity and therefore is not recommended. PCR has been used in research settings for the detection of a variety of organisms associated with BV, but evaluation of its clinical utility is uncertain. Detection of one organism or group of organisms might be predictive of BV by Gram stain. However, additional evaluations are needed to confirm these associations. Culture of *G. vaginalis* is not recommended as a diagnostic tool because it is not specific. Cervical Pap tests have no clinical utility for the diagnosis of BV because of their low sensitivity.

6.3 Treatment

Treatment is recommended for women with symptoms. The established benefits of therapy in nonpregnant women are to relieve vaginal symptoms and signs of infection. Other potential benefits to treatment include reduction in the risk for acquiring *C. trachomatis* or *N. gonorrhoeae*, HIV, and other viral STDs.

Recommended drugs: Metronidazole 500 mg orally twice a day for 7 days, Metronidazole gel 0.75%, one full applicator (5 g) intravaginally, once a day for 5 days; Clindamycin cream 2%, one full applicator (5 g) intravaginally at bedtime for 7 days.

7. Trichomoniasis

Trichomoniasis is caused by the protozoan *T. vaginalis*. (Nanda et al., 2006) Few men who are infected with *T. Vaginalis* might not have symptoms; others have NGU. Few women have symptoms characterized by a diffuse, malodorous, yellow-green vaginal discharge with vulvar irritation. However, many women have minimal or no symptoms. Because of the high prevalence of trichomoniasis in clinical and nonclinical settings, testing for *T. vaginalis* should be performed in women seeking care for vaginal discharge. Screening for *T. vaginalis* in women can be considered in those at high risk for infection (i.e., women who have new or multiple partners, have a history of STDs, indulge in sexual activity for payment, and use injection drugs).

7.1 Treatment

Metronidazole 2 g orally in a single dose or Tinidazole 2 g orally in a single dose or Metronidazole 500 mg orally twice a day for 7 days.

8. Vulvovaginal Candidiasis (VVC)

VVC is usually caused by *C.albicans*, but occasionally is caused by other *Candida* sp. or yeasts. Typical symptoms of VVC include pruritus, vaginal soreness, dyspareunia, external dysuria, and abnormal vaginal discharge. However, none of these symptoms is specific for VVC. An estimated 75% of women will have at least one episode of VVC, and 40%–45% will have two or more episodes within their lifetime. On the basis of clinical presentation, microbiology, host factors, and response to therapy, VVC can be classified as either uncomplicated or complicated. Approximately 10%–20% of women will have complicated VVC that necessitates diagnostic and therapeutic considerations.

8.1 Uncomplicated VVC

Diagnostic Considerations: A diagnosis of *Candida* vaginitis is suggested clinically by the presence of external dysuria and vulvar pruritus, pain, swelling, and redness. Signs include vulvar edema, fissures, excoriations, or thick, curdy vaginal discharge. The diagnosis can be made in a woman who has signs and symptoms of vaginitis when either 1) a wet preparation (saline, 10% KOH) or Gram stain of vaginal discharge demonstrates yeasts, hyphae, or pseudohyphae or 2) a culture or other test yields a yeast species. *Candida* vaginitis is associated with a normal vaginal pH (<4.5), and therefore, pH testing is not a useful diagnostic tool. Use of 10% KOH in wet preparations improves the visualization of yeast and mycelia by disrupting cellular material that might obscure the yeast or pseudohyphae. Examination of a wet mount with KOH preparation should be performed for all women with symptoms or signs of VVC, and women with a positive result should receive treatment. For women with negative wet mounts who are symptomatic, vaginal cultures for *Candida* should be considered. If the wet mount is negative and *Candida* cultures cannot be done, empiric treatment can be considered for symptomatic women with any sign of VVC on examination. Identifying *Candida* by culture in the absence of symptoms or signs is not an indication for treatment, because approximately 10%–20% of

women harbor *Candida* sp. and other yeasts in the vagina. VVC can occur concomitantly with STDs. Most healthy women with uncomplicated VVC have no identifiable precipitating factors.

8.2 Treatment

Short-course topical formulations e.g. Butoconazole 2% cream, Clotrimazole 2% cream, Miconazole 2% cream (i.e., single dose and regimens of 1-3 days) effectively treat uncomplicated VVC. The topically applied azole drugs are more effective than nystatin. Treatment with azoles results in relief of symptoms and negative cultures in 80%-90% of patients who complete therapy.

8.3 Complicated VVC

Recurrent Vulvovaginal Candidiasis (RVVC)

RVVC, usually defined as four or more episodes of symptomatic VVC in 1 year, affects a small percentage of women (<5%).(STD guidelines 2010) The pathogenesis of RVVC is poorly understood, and most women with RVVC have no apparent predisposing or underlying conditions. Vaginal cultures should be obtained from patients with RVVC to confirm the clinical diagnosis and to identify unusual species (including nonalbicans species), particularly *Candida glabrata*. Although *C. glabrata* and other nonalbicans *Candidia* species are observed in 10%-20% of patients with RVVC conventional antimycotic therapies are not as effective against these species as they are against *C. albicans*.

8.4 Treatment

Each individual episode of RVVC caused by *C. albicans* responds well to short-duration oral or topical azole therapy. However, to maintain clinical and mycologic control, some specialists recommend a longer duration of initial therapy (e.g., 7-14 days of topical therapy or a 100-mg, 150-mg, or 200-mg oral dose of fluconazole every third day for a total of 3 doses [day 1, 4, and 7]) to attempt mycologic remission before initiating a maintenance antifungal regimen.

Maintenance Regimens: Oral fluconazole (i.e., 100-mg, 150-mg, or 200-mg dose) weekly for 6 months is the first line of treatment. If this regimen is not feasible, topical treatments used intermittently as a maintenance regimen can be considered. Suppressing maintenance antifungal therapies are effective in reducing RVVC. However, 30%-50% of women will have recurrent disease after maintenance therapy is discontinued. Routine treatment of sex partners is controversial. *C. albicans* azole resistance is rare in vaginal isolates, and susceptibility testing is usually not warranted for individual treatment guidance.

Non albicans VVC

The optimal treatment of nonalbicans VVC remains unknown. Options include longer duration of therapy (7-14 days) with a nonfluconazole azole drug (oral or topical) as first-line therapy. If recurrence occurs, 600 mg of boric acid in a gelatin capsule is recommended, administered vaginally once daily for 2 weeks. This regimen has clinical and mycologic eradication rates of approximately 70%. If symptoms recur, referral to a specialist is advised.

	Normal	Vulvovaginal candidiasis	Trichomoniasis	Bacterial Vaginosis
Symptoms	None	Pruritis Soreness Dyspareunia	Soreness Dyspareunia Often asymptomatic	Often asymptomatic Occasional abdominal pain
Discharge Amount Color Consistency	Variable Clear/white Nonhomogenous flocular	Scant/moderate White Clumped, adherent	Profuse Green-yellow Homogenous, frothy	Moderate White/gray Homogenous adherent
Vaginal fluid pH	4.0-4.5	4.0-4.5	5.0-6.0	>4.5
Amine test (Fish odour)	None	None	Usually positive	Positive
Microscopy Saline	PMN:EC ratio <1 Lactobacilli predominate	PMN:EC ratio <1 Pseudohyphae (~40%)	PMN:EC ratio >1 Motile trichomonads PMNs predominate	PMN:EC ratio <1 Clue cells Coccobacilli
10% KOH	Negative	Pseudohyphae (~70%)	Negative	Negative

Table 3. Summary of clinical features of vaginitis (Wilson and Sande).

9. Pelvic Inflammatory Disease (PID)

PID comprises a spectrum of inflammatory disorders of the upper female genital tract, including any combination of endometritis, salpingitis, tubo-ovarian abscess, and pelvic peritonitis. Sexually transmitted organisms, especially *N. gonorrhoeae* and *C. trachomatis*, are implicated in many cases; however, microorganisms that comprise the vaginal flora e.g., anaerobes, *G. vaginalis*, *Haemophilus influenzae*, enteric Gram-negative rods, and *Streptococcus agalactiae*, also have been associated with PID. In addition, *M. hominis*, *U. urealyticum*, and *M. genitalium* might be associated with some cases of PID. All women who have acute PID should be tested for *N. gonorrhoeae* and *C. trachomatis* and should be screened for HIV infection. Symptoms of PID include abnormal cervical or vaginal discharge, abdominal pain and fever. On examination there may be cervical motion and adnexal and lower abdominal tenderness. It is important to diagnose and treat PID as early as possible. For patients requiring hospitalization, intravenous cefoxitin or cefotetan plus doxycycline (i/v or oral) can be given. Alternatively clindamycin plus gentamicin can be given followed by oral doxycycline. Outpatient treatments include oral ofloxacin plus metronidazole or ceftriaxone (or cefixitin and oral probenecid) plus oral doxycycline. Duration of intravenous treatment is dependent on the severity of the clinical presentation (Romanowski, 1993).

10. Epididymitis

In men under age 35, the most common pathogens are *N. gonorrhoeae* and *C. trachomatis* (Trojian et al., 2009). Homosexual men may have enteric pathogens from rectal intercourse. Unilateral testicular pain and tenderness are common. There is usually palpable swelling of the epididymis. The evaluation and diagnostic tests are the same as those for urethritis. Treatment includes ceftriaxone plus doxycycline or ofloxacin (Berger, 1991).

11. Proctitis

Proctitis acquired through receptive anal intercourse can be caused by *N. gonorrhoeae*, *C. trachomatis* (including LGV serovars), *T. pallidum* (syphilis) and HSV. Treatment includes ceftriaxone plus doxycycline.

12. Prevention

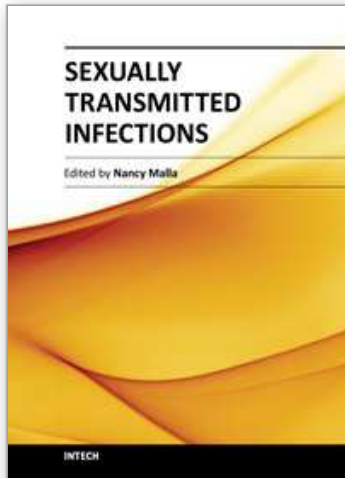
The most effective means to avoid becoming infected with or transmitting a sexually transmitted infection is to have sexual intercourse only within a long-term, mutually monogamous relationship with an uninfected partner and to abstain from sexual intercourse (i.e., oral, vaginal, or anal sex) with multiple partners. Male latex condoms, when used consistently and correctly, are highly effective in reducing the transmission of HIV and other sexually transmitted infections, including gonorrhoea, chlamydial infection and trichomoniasis. Prompt diagnosis and treatment of both the partners is the key for an effective management.

13. References

- Asin, J. (1952). Chancroid; a report of 1,402 cases. *Am J Syph Gonorrhea Vener Dis.* 36(5), 483-7.
- Bauwens, J. E., H. Orlander, M. P. Gomez, M. Lampe, S. Morse, W. E. Stamm, et al. (2002). Epidemic Lymphogranuloma venereum during epidemics of crack cocaine use and HIV infection in the Bahamas. *Sex Transm Dis.* 29(5), 253-9.
- Behets, F. M., J. Andriamiadana, D. Randrianasolo, R. Randriamanga, D. Rasamilalao, C. Y. Chen, et al. (1999). Chancroid, primary syphilis, genital herpes, and lymphogranuloma venereum in Antananarivo, Madagascar. *J Infect Dis.* 180(4), 1382-5.
- Berger, R. E. (1991). Acute epididymitis: etiology and therapy. *Semin Urol.* 9(1), 28-31.
- Bradshaw, C. S., S. N. Tabrizi, T. R. Read, S. M. Garland, C. A. Hopkins, L. M. Moss, et al. (2006). Etiologies of nongonococcal urethritis: bacteria, viruses, and the association with orogenital exposure. *J Infect Dis.* 193(3), 336-45.
- Brookes, J. L., S. Haywood and J. Green (1992). Prodromal symptoms in genital herpes simplex infection. *Genitourin Med.* 68(5), 347-8.
- Carlsson, B., H. S. Hanson, J. Wasserman and A. Brauner (1991). Evaluation of the fluorescent treponemal antibody-absorption (FTA-Abs) test specificity. *Acta Derm Venereol.* 71(4), 306-11.
- CDC fact sheet-syphilis: available at: <http://www.cdc.gov/std/syphilis/STDFact-Syphilis.htm>.

- CDC Sexually transmitted surveillance 2010. Available at:
<http://www.cdc.gov/std/stats10/other.htm>
- Chapel, T. A. (1980). The signs and symptoms of secondary syphilis. *Sex Transm Dis.* 7(4), 161-4.
- Clark, K. and J. Baranyai (1987). Pelvic infection and the pathogenesis of tubal ectopic pregnancy. *Aust N Z J Obstet Gynaecol.* 27(1), 57-60.
- Cone, R. W., A. C. Hobson, J. Palmer, M. Remington and L. Corey (1991). Extended duration of herpes simplex virus DNA in genital lesions detected by the polymerase chain reaction. *J Infect Dis.* 164(4), 757-60.
- Datta, S. D., L. A. Koutsky, S. Ratelle, E. R. Unger, J. Shlay, T. McClain, et al. (2008). Human papillomavirus infection and cervical cytology in women screened for cervical cancer in the United States, 2003-2005. *Ann Intern Med.* 148(7), 493-500.
- Dillon, S. M., M. Cummings, S. Rajagopalan and W. C. McCormack (1997). Prospective analysis of genital ulcer disease in Brooklyn, New York. *Clin Infect Dis.* 24(5), 945-50.
- Gaydos, C., N. E. Maldeis, A. Hardick, J. Hardick and T. C. Quinn (2009). *Mycoplasma genitalium* compared to chlamydia, gonorrhoea and trichomonas as an aetiological agent of urethritis in men attending STD clinics. *Sex Transm Infect.* 85(6), 438-40.
- Gottlieb, S. L., S. M. Berman and N. Low (2010). Screening and treatment to prevent sequelae in women with *Chlamydia trachomatis* genital infection: how much do we know? *J Infect Dis.* 15;(201 Suppl 2):S168-77.
- Greenblatt, R. M., S. A. Lukehart, F. A. Plummer, T. C. Quinn, C. W. Critchlow, R. L. Ashley, et al. (1988). Genital ulceration as a risk factor for human immunodeficiency virus infection. *Aids.* 2(1), 47-50.
- Holmes, K. K., P. J. Weisner and A. H. Pedersen (1971). The gonococcal arthritis-dermatitis syndrome. *Ann Intern Med.* 75(3), 470-1.
- Hosenfeld, C. B., K. A. Workowski, S. Berman, A. Zaidi, J. Dyson, D. Mosure, et al. (2009). Repeat infection with Chlamydia and gonorrhoea among females: a systematic review of the literature. *Sex Transm Dis.* 36(8), 478-89.
- Htun, Y., S. A. Morse, Y. Dangor, G. Fehler, F. Radebe, D. L. Trees, et al. (1998). Comparison of clinically directed, disease specific, and syndromic protocols for the management of genital ulcer disease in Lesotho. *Sex Transm Infect.* 74 Suppl 1S23-8.
- Johnson, S. R., D. H. Martin, C. Cammarata and S. A. Morse (1994). Development of a polymerase chain reaction assay for the detection of *Haemophilus ducreyi*. *Sex Transm Dis.* 21(1), 13-23.
- Johnson, S. R. and S. A. Morse (1988). Antibiotic resistance in *Neisseria gonorrhoeae*: genetics and mechanisms of resistance. *Sex Transm Dis.* 15(4):217-24.
- Keat, A. (1999). Reactive arthritis. *Adv Exp Med Biol.* 455:201-6.
- Khan, S. A., F. Amir, S. Altaf and R. Tanveer (2009). Evaluation of common organisms causing vaginal discharge. *J Ayub Med Coll Abbottabad.* 21(2), 90-3.
- Larsen, S. A., B. M. Steiner and A. H. Rudolph (1995). Laboratory diagnosis and interpretation of tests for syphilis. *Clin Microbiol Rev.* 8(1), 1-21.
- Liu, H., B. Rodes, C. Y. Chen and B. Steiner (2001). New tests for syphilis: rational design of a PCR method for detection of *Treponema pallidum* in clinical specimens using unique regions of the DNA polymerase I gene. *J Clin Microbiol.* 39(5), 1941-6.

- Livengood, C. H. (2009). Bacterial vaginosis: an overview for 2009. *Rev Obstet Gynecol.* 2(1), 28-37.
- Manhart, L. E., K. K. Holmes, J. P. Hughes, L. S. Houston and P. A. Totten (2007). *Mycoplasma genitalium* among young adults in the United States: an emerging sexually transmitted infection. *Am J Public Health.* 97(6), 1118-25.
- Morgan, E. D., J. D. Laszlo and P. G. Stumpf (1988). Incomplete Behcet's syndrome in the differential diagnosis of genital ulceration and postcoital bleeding. A case report. *J Reprod Med.* 33(10), 844-6.
- Nanda N, Michel RG, Kurdgelashvili G, Wendel KA (2006). Trichomoniasis and its treatment. *Expert Rev Anti Infect Ther.* 4(1):125-35.
- O'Farrell, N. (2002). Donovanosis. *Sex Transm Infect.* 78(6), 452-7.
- Pandhi, R. K., A. S. Kumar, D. A. Satish and L. K. Bhutani (1984). Fixed drug eruptions on male genitalia: clinical and etiologic study. *Sex Transm Dis.* 11(3), 164-6.
- Pellati, D., I. Mylonakis, G. Bertoloni, C. Fiore, A. Andrisani, G. Ambrosini, et al. (2008). Genital tract infections and infertility. *Eur J Obstet Gynecol Reprod Biol.* 140(1), 3-11.
- Romanowski, B. (1993). Pelvic inflammatory disease. Current approaches. *Can Fam Physician.* 39:346-9.
- Solomon, A. R., J. E. Rasmussen and J. S. Weiss (1986). A comparison of the Tzanck smear and viral isolation in varicella and herpes zoster. *Arch Dermatol.* 122(3), 282-5.
- STD Trends in the United States: 2010 National Data for Gonorrhea, Chlamydia, and Syphilis. Available at: <http://www.cdc.gov/std/stats10/trends.htm>
- STD guidelines 2010: Diseases characterized by vaginal discharge. Available at: <http://www.cdc.gov/std/treatment/2010/vaginal-discharge.htm#a3>
- Su, W. H., T. S. Tsou, C. S. Chen, T. Y. Ho, W. L. Lee, Y. Y. Yu, et al. (2011). Diagnosis of Chlamydia infection in women. *Taiwan J Obstet Gynecol.* 50(3),261-7.
- Svenstrup, H. F., J. Fedder, S. E. Kristoffersen, B. Trolle, S. Birkelund and G. Christiansen (2008). *Mycoplasma genitalium*, Chlamydia trachomatis, and tubal factor infertility--a prospective study. *Fertil Steril.* 90(3), 513-20.
- Taylor-Robinson, D., C. B. Gilroy, B. J. Thomas and P. E. Hay (2004). *Mycoplasma genitalium* in chronic non-gonococcal urethritis. *Int J STD AIDS.* 15(1), 21-5.
- Temmerman, M. (1992). Sexually transmitted diseases and reproductive health. *Prog Hum Reprod Res.* (21), 6-7.
- Trees, D. L. and S. A. Morse (1995). Chancroid and *Haemophilus ducreyi*: an update. *Clin Microbiol Rev.* 8(3), 357-75.
- Trojan, T. H., T. S. Lishnak and D. Heiman (2009). Epididymitis and orchitis: an overview. *Am Fam Physician.* 79(7), 583-7.
- Veeranna, S. and T. Y. Raghu (2003). A clinical and investigational study of donovanosis. *Indian J Dermatol Venereol Leprol.* 69(2), 159-62.
- (WHO fact sheet 2011). available at <http://www.who.int/mediacentre/factsheets/fs110/en/>.
- WHO (2011). http://www.who.int/hiv/pub/progress_report2011/summary_en.pdf.
- Wilson, W. R. and M. A. Sande Current diagnosis and treatment in infectious diseases. United States of America: The McGraw-Hill Companies; 2001. Chapter 15, Sexually Transmitted Diseases; p.203-19.
- Wright, R. A. and F. N. Judson (1979). Penile venereal edema. *Jama.* 241(2), 157-8.



Sexually Transmitted Infections

Edited by Prof. Nancy Malla

ISBN 978-953-51-0258-8

Hard cover, 244 pages

Publisher InTech

Published online 21, March, 2012

Published in print edition March, 2012

Sexually transmitted infections (STIs) are infections that are spread primarily through person to person sexual contact. There are more than 30 different sexually transmissible bacteria, viruses and parasites. STIs lead to high morbidity and complications. This book entitled as Sexually Transmitted Infections is not a text book but provides useful information for general reference work for physicians, researchers and students interested in the subject. Each chapter is abundant in tips useful to general readers as well. It also includes the Introductory chapter providing an overview with special emphasis on syndromic approach to the management of STIs in clinical setting.

How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Nancy Malla and Kapil Goyal (2012). Sexually Transmitted Infections: An Overview, Sexually Transmitted Infections, Prof. Nancy Malla (Ed.), ISBN: 978-953-51-0258-8, InTech, Available from:
<http://www.intechopen.com/books/sexually-transmitted-infections/sexually-transmitted-infections-an-overview>

INTECH
open science | open minds

InTech Europe

University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
www.intechopen.com

InTech China

Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

© 2012 The Author(s). Licensee IntechOpen. This is an open access article distributed under the terms of the [Creative Commons Attribution 3.0 License](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

IntechOpen

IntechOpen