Viral, bacterial and fungal infections of the oral mucosa. Types: Incidence; predisposing factors; diagnostic algorithms; management

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Abstract
For millions of years, microbiota residing within us, including those in the oral cavity coexisted in a harmonious symbiotic fashion that provided a quintessential foundation for human health. It is now clear that disruption of such a healthy relationship leading to microbial dysbiosis causes wide array infections ranging from localized, mild, superficial infections to deep, disseminated life-threatening diseases. With recent advances in research, diagnostics and improved surveillance we are witnessing an array of emerging and re-emerging oral infections and orofacial manifestations of systemic infections. Orofacial infections may cause significant discomfort to the patients and unnecessary economic burden. Thus, the early recognition of such infections, is paramount for holistic patient management, and oral clinicians have a critical role in recognizing, diagnosing, managing and preventing, either new or old, orofacial infections. This chapter aims to provide an update on current understanding of well established and emerging viral, bacterial and fungal infections manifesting in the human oral cavity.

Introduction

Skin and the mucous membranes in the orofacial region are often affected by a diverse spectrum of bacterial, viral, fungal, chlamydial, rickettsial, protozoal and helminthic infections. Such conditions may clinically appear as small, localized lesions to diffuse and invasive varieties that extend beyond natural barriers, often causing potentially life-threatening complications. Partly due to the narrow geographical distribution and effective preventive strategies in much of the world, few clinicians will have personally examined or be familiar with the clinical presentations and laboratory investigations of some of the orofacial infections described here.

Regardless of the prevalence, incidence and the advancement of treatment strategies, orofacial infections, either local or the manifestations of a generalized infection, may cause significant discomfort and suffering. Thus, the recognition of the clinical presentation of these infections is paramount to their diagnosis, clinical management and appropriate referral. A critical assessment of clinical signs and symptoms, likelihood of individual and communal predisposition, the past medical, dental and social history, appropriate sampling, and accurate interpretation of the laboratory results are all essential in determining definitive diagnoses and management protocols. Therefore, in this chapter, we discuss the types, incidence, predisposing factors, diagnostic algorithms and management of common orofacial infections of viral, bacterial, and fungal origin.

Viral infections

Human Herpes viruses

Although many viruses can infect the oral cavity, members of the human herpesvirus (HHV) family cause the most common viral infections with variable clinical presentations. All herpesviruses are structurally similar (enveloped, icosahedral with double-stranded DNA) and they infect both humans and animals. Additionally, all herpesviruses are neurotropic and have the important property of remaining latent, with the ability to reinfect the host and cause recurrent infection a variable period after the primary infection.

A range of different human herpesviruses have bene identified and they are numbered 1–8. HHV1 (also called herpes simplex-1, HSV1) causes oral and genital herpes (predominantly orofacial). HHV2 (Herpes simplex virus-2, HSV2) also causes oral and genital herpes simplex, however genital manifestations are predominant. The primary infection of varicella zoster virus (HHV3, VSV) is chicken pox and the reactivation of the virus results in shingles. HHV4, also called Epstein Barr virus (EBV) is known to cause Infectious mononucleosis, Burkitt's lymphoma, and CNS lymphoma in AIDS patients. Oral hairy leukoplakia, first identified in people with HIV disease, is also caused by EBV. Individuals infected with Cytomegalovirus (CMV), the 5th HHV, exhibit

infectious mononucleosis like symptoms. Roseolovirus (HHV6) and HHV7 cause a similar infection known as roseola infantum or exanthem subitum. HHV8 mainly causes Kaposi's sarcoma and primary effusion lymphoma, thus it is called Kaposi's sarcoma-associated herpesvirus (KSHV) (154).

Following section describes orofacial manifestations of HHV1 to HHV3. Epstein Barr virus (HHV4) and cytomegalovirus (HHV5) infections are summarized in Table 2.

Herpes simplex infections (HHV1 and 2)

Epidemiology

Children between 6 months to 3 years of age are at higher risk to expose to HSV1 through direct contact with another individual carrying HSV1. Approximately 60% of the population has been infected By 14-49 years of age, and the infected population rises up to 80%-85% by the age of 60 years (55). HSV2 is one of the most common sexually transmitted disease and approximately 17% of the US adults between 14 to 49 years of age are chronically infected with HSV-2 (86, 167). Alarmingly, 95% of HSV-2 seropositive individuals estimated to be shedding HSV-2 asymptomatically (49). Recent reports suggested that, in western countries, the incidence of HSV-1 in children is decreasing and many are exposed to HSV-1 for the first time during their adolescence as a result of an active sexual lifestyle (123).

Predisposing factors

Children between 6 months to 3 years are of high risk for HSV1 exposure. Specially through kissing, touching the person's skin, such as pinching a child's cheek and sharing objects such as silverware, lip balm, or a razor can predispose an individual to expose to HSV1.

The susceptibility to HSV2 infection is higher among females. In addition, individuals who have had many sex partners, had sex for the first time at a young age, have (or had) another sexually transmitted infection and have a weakened immune system due to a disease or medicine are more prone to be infected with HSV2. However, greater HIV/HSV-2 coinfection rates were estimated among heterosexuals in sub-Saharan Africa and men who have sex with men (MSM) in the Americas (27, 96, 187, 243).

Recurrent herpes infections commonly diagnosed in patients receiving cancer chemotherapy or immunosuppressive drugs to prevent graft rejection after transplantation or with advanced AIDS (215, 216).

Pathogenesis of Herpes simplex infections

Herpes simplex viruses enter host cell by interacting their surface glycoproteins (glycoprotein B, C, D, H and L) with various host cell surface receptors (14, 235). Alternatively, HSV may enter the host cell via endocytosis (148, 161). Regardless of the method of entry, viral membrane fuse with host cell membrane to facilitate the entry of viral capsid and accompanying tegument (viral proteins) into the cytoplasm (62). Subsequently, the viral capsid released to host cell cytoplasm reaches the outer nuclear membrane by linking tegument to host cell microtubules. Viral capsid binds to the host nuclear pore complex and release the viral DNA into the host nucleus (62, 93). Using host RNA-polymerase II, viral DNA are sequentially transcribed (59, 100) in order to encode for proteins required to evade host immunity, replicate viral DNA, synthesize structural components of virions, including tegument, capsid, and other surface proteins (46, 180). Capsid proteins synthesized in the cytoplasm migrate in to the nucleus and assemble with newly transcribed viral DNA to create new virions (98). Consequently, the capsid travels to cytoplasm and is coated with additional tegument proteins and enveloped in the trans-Golgi network (234). Finally, the virions are carried to cell surface via vesicles and secreted. In contrast, some evidence

has shown that HSV are capable of propagating to adjacent cells directly via cell-cell interactions, particularly when infecting T cells (13, 113).

As a well evolved virus, HSV targets multiple host immune components to evade immune response. These host components include antibodies, natural killer cells, complement proteins and, major histocompatibility complex class I or II molecules (104, 130). Once the primary HSV infection is established, HSV internalize by fusing the viral envelope with neuronal cell at sensory nerve terminals and travel to trigeminal nerve ganglion via retrograde axonal transport. HSV reside within trigeminal nerve ganglion and may reactivate when appropriate triggering factors (134, 162). Once reactivated, viruses travel along the neurons and develops secondary infection in relevant dermatomes.

Clinical presentation

Classically, HSV1 is known to cause infections above the waist including oral and pharyngeal infection, meningoencephalitis, and dermatitis while HSV2 causes infections below the waist such as genital and anal infections. However, both viruses have been isolated in primary or recurrent infections in the oral, perioral, or genital area as a result of different sexual practices (215, 216).

Primary infection

In most cases of HSV infections, patients experience prodromal symptoms such as burning, itching or tingling sensations of the skin or mucosa for a day or so (215, 216).

Primary HSV infection appears with systemic symptoms, which may include fever, headache, malaise, nausea, vomiting, and accompanying lymphadenopathy (80, 79). Usually HSV infections are subclinical or may cause pharyngitis. As a result, it is often misdiagnosed as an upper respiratory tract infection. Oral lesions appear on the lip or around the mouth, less frequently in the tongue, palatal and buccal mucosae and the face. The blisters or vesicles erupt as clusters and ooze with a clear to yellowish fluid that may develop into a yellowish crust. These eruptions are extremely painful and break down rapidly and appear as tiny, shallow grey ulcers on a red base. Subsequently, they become crusted or scabbed and appear drier and more yellow in several days (55). Primary herpetic gingivostomatitis also manifest as vesicles and ulcers on the oral mucosa and in marginal gingiva causing acute generalized marginal gingivitis. The ulcers cause intense erythema in the gingiva and possible bleeding (215, 216). Cervical lymphadenopathy is a common finding in HSV infections (55).

Recurrent infections

Upon recovery from the clinical infection, the virus could become dormant in trigeminal ganglion. Reactivation of this latent virus can result recurrent herpes infections. Reactivation is usually triggered by exposure to cold, sunlight, traumatic events, stress or immune suppression (215, 216). The most common manifestation of the recurrent HSV infection is herpes labialis which typically appear in the mucocutaneous junction of the lip, often referred to as cold sores or fever blisters (Figure 1). Herpes labialis also exhibit burning or tingling sensations of the site of future blisters. Small fluid filled semi translucent blisters appear in the lips and may coalesce to form a large blister. Blisters dry out within several days resulting a scab formation (55).

Diagnosis

When the clinical infection is present, diagnosis is made mainly with clinical presentation. However, laboratory tests may be necessary to confirm and to establish the diagnosis of atypical presentations (219). These include virologic tests in which the presence of the virus is confirmed by the cytopathic changes in a tissue culture infected with the virus (215, 216). In addition, cytology smears stained with Giemsa or Papanicolaou stain are used to identify the characteristic cytopathic and viral features in the suspected smear (15). Immunological tests such as direct fluorescent assay, detection of viral DNA through PCR assays (the test of choice for HSV) and

serological tests to detect anti HSV antibodies in serum are commonly used in HSV diagnosis (48, 76, 220).

Treatment
The treatment for primary infection is usually palliative. Mild cases of the infection is managed by supportive care which includes adequate hydration, pain and fever management with analgesics and antipyretics, topical anaesthetics such as viscous lidocaine or a mixture of liquid benadryl, milk of magnesia, and carafate to decrease oral pain (217, 218). Antiviral therapy with Aacyclovir, Valacyclovir and Famicyclovir are proven to reduce the symptoms if started within 24-48 h of vesicle eruption (8, 16, 80, 79).

Recurrent infections in otherwise healthy patients are also treated symptomatically. and patients with chronic immune suppression, or with severe, painful, or deforming recurrent herpes may require systemic antiviral medications (192).

HHV3 Primary infection: Varicella Zoster

Epidemiology
Varicella zoster infection is prevalent worldwide. Prevalence in adults is higher than in children. The occurrence is higher in tropical countries compared to other climates. Varicella exhibits classical seasonal fluctuations in temperate climates with the highest incidence of the infection occurring in winter and early spring. The seasonal variations are less commonly experienced in tropical areas (39).

Predisposing factors
New born babies, specially within first 28 days of life, pregnant women who have not been exposed to chicken pox before and immunocompromised individuals such as those with leukaemia or Hodgkin's disease, or those taking immunosuppressive medications, are at higher risk of developing longer and more serious illness (24). Varicella is extremely contagious and the risk of secondary attack among susceptible household contacts is as high as 90% (39)

Clinical presentation
Chicken pox is a benign infection in childhood. It spreads by direct contact with an infected individual, especially with skin lesions or nasopharyngeal secretions (215, 216). Symptoms of the infection usually appear after 10-21 days of an incubation period.

Skin lesions are intensely pruritic and maculopapular in appearance. The rash rapidly develop in to fluid filled vesicles with an erythematous base ('dew drop on a rose petal'). Oral lesions, mainly vesicles and ulcers, are similar to those appear in HSV infections and commonly seen on the palate, pillars of fauces and uvula (192).

Diagnosis
Clinical presentation of the infection is pathognomonic. When symptoms are not present, identification of viral DNA in serum, saliva or CSF aids diagnosis (192).

Treatment
Management of chickenpox is symptomatic such as adequate hydration, bed rest, fever control by paracetamol (aspirins should be avoided). Lukewarm baths and lotions are useful to reduce itching (24). However, in severe cases, antiviral therapy is recommended.

Despite multiple attempts made for developing vaccines against HSV infections during last 2 decades, the success of such trials appeared to be minimal and appeared ineffective in either preventing the occurrence or shedding the virus (183, 255), usage of viral subunits raised concern about potentially developing infection and application of neutralizing antibodies instead,

have also been under discussion. However, in a recent trial, a vaccine containing HSV-2 glycoprotein D showed superior effect against HSV-1 induced genital infections compared to HSV-1 infections in the same site (21, 32, 94, 183, 255). While latter finding encourages to think that promising vaccines against HSVs are likely to be a reality than expected, the field of novel microbicides against HSVs is promising and is likely to generate agents that can cure the infection permanently (221).

HHV3 reactivation: Herpes Zoster

Epidemiology

Herpes zoster (Shingles) is a sporadic disease and the lifetime incidence is estimated to be 10-20%. Incidence of shingles rises with aging and doubled in each decade past the age of 50 years. Approximately, in the USA, 50% of persons living until age of 85 years will develop zoster (39). There is 15 times higher incidence of shingles in HIV infected patients compared to uninfected while blacks are one fourth as likely as whites to develop herpes zoster. There is 15% household transmission rate (6, 201, 208, 214). The lifetime risk of herpes zoster is estimated to be at least 32%. Herpes zoster has no seasonal variation and may be reported throughout the year.

Predisposing factors

Patients who have had varicella zoster, those who are older than 50 years, compromised immune status e.g. HIV, diabetes, under steroids or cytotoxics or suffering from cancer are at high risk of having shingles. Stress and trauma are also known precipitation factors (214).

Clinical features

The initial symptoms range from pain, tenderness, and paraesthesia along the course of the affected nerve. Vesicles appear unilaterally after 3-5 days in the dermatome supplied by the affected nerve. Vesicles have inflamed bases. When facial nerve (geniculate ganglion) is affected, lesions appear unilaterally along the external ear, face and oral mucosa. Unilateral facial paralysis is not uncommon causing Ramsey-Hunt syndrome (215, 216). Herpes zoster can affect the motor nerves occasionally. Ophthalmic, maxillary or mandibular branches of the trigeminal nerve can be affected, and this results in painful skin lesions as well as intraoral lesions along the course of the affected branch (Figure 2). Intraoral lesions are intensely painful (192).

Post herpetic neuralgia may develop as a consequence of herpes zoster due to scarring of the involved nerve during the infection (215, 216). Post herpetic neuralgia is intensely painful and debilitating condition which may last for many months to years.

Diagnosis

Diagnosis is based on clinical presentation. Laboratory tests may be necessary for less typical presentations. These tests include direct fluorescent antibody staining of varicella-zoster virus (VZV)-infected cells, polymerase chain reaction (PCR) can be used to detect VZV DNA, serologic tests (However, it is difficult to distinguish herpes zoster from varicella zoster by serologic tests) (37). One study showed that the sensitivity and specificity of detecting VZV DNA in cells from the base of lesions after they are unroofed by PCR was 95-100% whereas immunofluorescent tests in detecting viral antigens were only 82% sensitive and 76% specific (198). When there is a systemic involvement, PCR assays are used to detect viral DNA in cerebrospinal fluid (CSF) and blood. It has been recently shown that elevated ratio of anti VZV antibody level in CSF to blood is a more sensitive parameter in diagnosing central nervous system involvement of VZV (91).

Treatment

Antiviral drugs speed healing of the lesions and reduce the duration of severe pain (Valacyclovir 1g three times a day for 7-10 days). Intravenous acyclovir is required for immunocompromised patients. Short courses of corticosteroids such as oral prednisone are often used to control the

inflammatory response associated with severe pain (90). In addition to anti-viral therapy and corticosteroids, post herpetic neuralgia is treated with gabapentin, tricyclic antidepressants, opioids, topical capsaicin and topical lidocaine patches to assist with pain control (66, 215, 216).

Other Oral Viral Infections

The foregoing describes only the most frequent oral viral infections belonging to the herpes group of viruses. Yet dentists frequently see patients with an assortment of infections caused by RNA viruses such as the Rhinovirus (common cold virus), influenza virus, coxsackie virus (hand, foot and mouth disease) measles and mumps virus. These infections may or may not present with oral manifestations but are important in the context of infection control aspects of dentistry.

There, are new viral infections re-emerging and emerging incessantly in different regions of the World, such as the recent Ebola virus outbreak and Zika virus infection in Africa and South America, respectively. Increase in host susceptibility due to poor personal and social hygiene, overcrowding, societal breakdowns such as wars and civil chaos, poverty and lack of public healthcare and, human factors including sexual and substance abuse activities can create favorable environments for new and re-emerging viral infections (126). Natural mutations of viruses that increase viral virulence (e.g. Influenza), geographical transfer of viruses to distinct human populations (e.g. Chicangunya) and viruses crossing the species-specific barriers (e.g. SARS, HIV and Ebola) also have major impact on emerging new infections. Though there is lack of reports on oral manifestations of the new, re-emerging viral infections, it is still too early to exclude the potential of oral complications of these diseases. The Table 1 provides a guide to some of these infrequent viral infections that may manifest in the oral cavity.

With emerging new infections as well as isolation of mutant and drug resistant variants of existing viral pathogens, specific and sensitive diagnosis are of paramount importance in managing existing infections and preventing further individual and communal dissemination. The new era of clinical virology is moving towards highly specific new generation diagnostic tools such as nucleic acid amplification tests, real time quantitative PCRs, next generation sequencing, and mass spectrometry. These technologies not only possess extreme sensitivity and specificity, low detection limits, but also produce fast and automated results facilitating early interventions (210).

Bacterial infections

Actinomycosis

Incidence

Actinomycosis is an infrequent invasive bacterial disease caused by *Actinomyces* species. These are filamentous anaerobic Gram-positive bacilli, commonly isolated in the human commensal flora of the oropharynx, gastrointestinal tract, and urogenital tract (236). Orofacial structures, respiratory tract, bone and joint, genitourinary tract, gastrointestinal tract, central nervous system, skin, and soft tissue structures can be affected with actinomycosis (139, 207, 248). Though there are over 30 *Actinomyces spp.* described, *Actinomyces israelii* is the most isolated species in clinical disease of man (73, 139, 176, 207, 248). Occasionally, *Actinomyces viscosus* and *Actinomyces meyeri* are also reported (81, 176).

Human oropharynx, tonsillar crypts, gingival crevices, periodontal pockets and dental plaque both supra- and sub- gingival plaque biofilms), and carious teeth harbor *Actinomyces* as orofacial commensal flora (139, 207, 248). Thus, actinomycosis in the orofacial region (also called "lumpy jaw syndrome") is considered to have endogenous origin. Actinomycosis in the orofacial region

(also known as cervicofacial actinomycosis) is the most frequent clinical form of actinomycosis, representing approximately 60% of all reported cases (139, 164, 207, 248). Patients with odontogenic maxillary sinusitis may be infected with *Actinomyces* leading to maxillary osteomyelitis (190). Although more than 30 species of *Actinomyces* have been identified, over 70% of oro-cervicofacial infections are caused by *A. israelii* and *A. gerencseriae* (formerly *A. israelii* serotype 2) (176).*A. meyeri, A. odontolyticus, A. naeslundii, Actinomyces georgiae, Actinomyces pyogenes, or A. viscosus* have also been isolated in some cases (176). Although most infections are monomicrobial in nature (i.e. with *Actinomyces* alone causing the disease), a significant proportion of infections could be polymicrobial, with other bacteria such as *Aggregatibacter actinomycetemcomitans*, *Haemophilus spp.* and anaerobes acting as co-infecting agents (192).

Predisposing factors

Over 80% of actinomycosis cases were reported in young adults over 20 years of age despite others have noted that actinomycosis can primarily affect from the 3rd to 6th decades of life (69). When children are affected, it rarely spread beyond cervicofacial lesions (22). Local predisposing factors of actinomycosis include poor oral hygiene (dental caries, gingivitis and teeth with gangrenous pulps and pericoronitis) and traumatic events to oral mucosa including dental extraction, gingival trauma, irradiation, neoplasms and cervicofacial surgery. Men are more susceptible than women for reasons that are unclear. Several early studies suggested that there were significant 3:1 to 4:1 predilection among male population compared to females to cervicofacial actinomycosis, however, consequential studies have shown that there are no sexual or racial predisposition to actinomycosis as the infection mainly disseminated through orofacial trauma with mucosal rupture (69, 132, 147).Those with uncontrolled diabetes mellitus, immunosuppression, alcoholism, and malnutrition are also more prone to actinomycosis. (101, 111, 139, 176, 207, 248, 251). However, in an early study, Lerner et al noted that the association of immunocompromised status due to leukemia, renal failure, metastatic carcinoma, or AIDS with the susceptibility to actinomycosis marginal (132, 229).

Pathogenesis

Actinomyces carries a very low potential for virulence and remains mostly as an oral commensal. The bacterium is considered neither opportunistic nor communicable. The onset of actinomycosis appeared to be multifactorial as depicted by its unpredictable association with the extent of the mucosal breach. For instance, actinomycosis can develop after minor oral mucosal trauma, as in a simple tooth eruption whereas in other cases, even with significant orofacial lacerations, there are no reported incidence of actinomycosis (147). In addition, the repeated exposure of the site of mucosal trauma to Actinomyces also considered an important determinant of actinomycosis onset (229).

Actinomyces prefer low oxidoreductive environments, thus, the bacterium inhabits polymicrobial communities that create favoring anaerobic niches. During pathogenesis, Actinomyces destroy highly vascularized mucosal tissues and replace with poorly irrigated and scarcely vascularized granulated tissues which, in turn, further support the bacterial growth providing favorable low oxygen tension. Actinomycotic granuloma are histopathologically presented as isolated granulomatous inflammatory lesions with suppurative central necrosis or isolated foci of suppurative necrosis. Filamentous Sulphur granules develop in necrotic foci as characteristic "sunburst radiation" or furry appearance (132). Sulphur granules is mineralized host calcium phosphate produced during surrounding tissue inflammation. Ends of the Sulphur granules may provide adhesion sites for neutrophils or polymorphonucleocytes to form club-shaped extensions or rosettes (132). Actinomyces bacteria can be seen within the aggregates of sulphur granules as well as outer margin of necrotic core (132). The outer surface of the lesion is covered with lipoid cells and encased in inflammatory cell populations consisting of lymphocytes,

epithelioid cells, plasma cells, and histiocytes and occasionally giant cells (22). The lesion is limited with a remarkably avascular, collagenous and fibrotic tissue. The lesion can expand to surrounding tissues slowly with time when there are no bony impediments (22).

Clinical presentation

Cervicofacial actinomycosis commonly affects the submandibular region and rarely the maxillary antrum, salivary glands and tongue (192). Approximately 50% of cases affect the mandible itself and the remaining affected areas include cheek (15%), chin (15%), and submaxillary ramus and angle (10%) (199). Other non-odontogenic orofacial locations such as the tongue, paranasal sinuses, middle ear, larynx, lachrymal pathways, and thyroid gland may rarely be affected (12, 115, 122, 195, 239).

Typical presentation of the disease is a slow growing painless indurated localized or diffuse mass which could lead to multiple abscesses with discharging sinuses to skin or oral mucosa. Classically, the discharge contains visible granules that are gritty to touch, yellow and are known as 'sulphur granules' (a descriptive term, as sulphur is not found). These granules in pus are almost pathognomonic of the disease. Pain and trismus may occur in the advanced stage. Acute suppurative episodes present with fever and pain. Fibrosis around the swelling and the involvement of infected teeth are common. Bone involvement is observed in approximately 10% of cases and regional adenopathy is rare (131, 139, 164, 199, 207, 248).

Diagnosis.

Dental panoramic radiograph is mandatory to assess apical lesions and CT scan and MRI may be useful to assess any extensive bone involvement (197). If a fluctuant abscess is present, aspiration biopsy must be conducted to examine pus for the presence of 'sulphur granules'; the crushed granules are cultured anaerobically for 7 days to observe colonies of typical 'molar tooth' morphology (Figure 3). Biopsies stained with hematoxylin and eosin and special stains such as Gomori methenamine silver, p-aminosalicylic acid, McCallen-Goodpasture, and Brown-Benn facilitate the identification in histopathological sections (164). A Gram staining of a colony will reveal moderate to large clumps of Gram-positive branching filaments (192). It is important that specimens are collected and transported anaerobically and, cultured in strict anerobic environment for up to 14 days in liquid or solid media such as thioglycolate liquid media, brain heart infusion or blood agar (147). Pure cultures are needed to be identified using immunological techniques using monoclonal antibodies (164).

With other pathological conditions such as tuberculosis, systemic mycoses, nocardiosis, periodontal abscess, and dentoalveolar abscess that exhibit similar clinical manifestations, the diagnosis of orofacial actinomycosis can be challenging (139, 207, 248). Particularly, early prescriptions of antimicrobial prior to surgeries may complicate the pathogen identification resulting false negative findings. Thus, it is usually recommended that discontinuation of antimicrobial therapy two weeks prior to facilitate bacterial growth in cultures isolated from patients with chronic mandibular osteomyelitis suspected to have cervicofacial actinomycosis. However, patients with lumpy jaw syndrome have always been prescribed anti-actinomycotic drugs regardless of the microbiological test findings (236).

Management

Acute lesions are managed by removal of any associated dental focus, often necessitating dental extractions, incision and drainage of the facial abscesses and a 2–3-week course of antibiotics - penicillin being the drug of choice. However, poor vascularity and solid capsule may delay/hinder the penetration of antibiotics, penicillin in particular, in to the lesion (45). In case of penicillin

hypersensitivity, erythromycin, tetracycline and clindamycin are considered good alternatives as they are claimed to penetrate hard tissues (22, 124).

In the case of subacute or chronic voluminous lesions surgical interventions such as marsupialization or excision and/or debridement of necrotic bone are indicated (29, 139, 164, 207, 248). Though there are no reliable data on randomized control clinical trials on antibiotic treatment regimens on chronic cervicofacial actinomycosis, longer antibiotic course up to 6 weeks may be necessary for those who are chronically affected and surgically treated. New concepts of adjunct therapy of antimicrobial agents, particularly beta lactamase inhibitors and metronidazole with forgoing antibiotics are emerging, however, their efficacy is yet to be fully established (223).

Syphilis

Incidence

Syphilis caused by *Treponema pallidum* is a relatively common sexually transmitted infection. In 2008, 36.4 millions of infected adults and 10.6 new cases of syphilis were reported worldwide (246) (38). Syphilis was frequent in the early 1900s and was a leading cause for heart and neurological diseases (118, 196, 238). There was a progressive reduction of the prevalence of syphilis and in 2000/2001, it lowest prevalence was reported (2.1 cases per 100, 000 population) the USA (9, 65, 119, 158) (38). However, during the last two decades, the disease has been resurgent in countries in North America, Europe, Russia and China (9, 31, 65, 105, 119, 155, 158, 188, 227, 238). For instance, Primary and secondary syphilis rate increased to 6.3 cases per 100, 000 in the USA in 2015 (38). Sexual promiscuity, decreasing use of barrier protection (i.e. condoms), and HIV co-infection are blamed for the change in the syphilis epidemiology (192).

Predisposing factors

More than 50-60% new cases are reported among men who have sex with men (MSM, i.e. gay, bisexual, and other men who have sex with men). HIV infection, high risk sexual behaviors, drug abuse, increased travel and migration that indirectly increase the prevalence of HIV and other Sexually transmitted infections (STI), low education and alcohol use are associated with the increase in the incidence of syphilis (25, 31, 118, 152, 188, 227).

Pathogenesis

Despite a large number of in vivo studies have been reported in animal models, the data on syphilis pathogenesis in humans are limited. This is likely due to the ethical considerations of clinical trials of syphilis in human subjects. *T. pallidum* is assumed to penetrate in to the body through various degrees of skin or mucosal membrane breaches (83, 137, 138). As evidenced in some animal and human studies, the incubation period and onset of the primary syphilis are determined by the size of the initial inoculum of the pathogen (135, 136). Once entered through the skin/epithelial barrier, *T. pallidum* rapidly disseminate to lymph nodes brain, and aqueous humor, and in the CSF other distal organs within hours (51, 178, 179). Infected rabbit and human tissue samples have confirmed that *T. pallidum* is capable of attaching to a wide variety of cell types including epithelial, endothelial and fibroblast-like cells (84, 95, 129, 226).

Due to the specific bacterial adhesin- host ligand interactions, it is said that the number of bacteria that can attach per host cell is limited despite the size of inoculum is an important parameter of the onset of the infection as mentioned above (95, 103, 178). Until recently, the mechanism of *T. pallidum* attachment to cells were ill-understood, however, recent studies have indicated that tpr family of genes encode proteins that facilitate attachment to host tissue (40, 178). It is believed that host cell integrins act as the host ligands for the treponemes (129). Interestingly, a tpr protein, Tpr K is targeted by host opsonic antibodies and the opsonized *T. pallidum* can be

phagocytosed by activated macrophages (127, 151). However, it is argued that these proteins show antigenic variations through gene conversions to avoid host immune response. Such theories are yet to be established (19, 41, 103, 178, 225, 224). *T. pallidum* is considered highly invasive and its motile nature facilitate this essentially critical virulence factor. *T. pallidum* is shown to penetrate endothelial cell monolayers and intact membranes with extreme efficacy (184, 226).

Irrespective of the stage, all syphilitic lesions are exhibit characteristic endarteritis and periarteritis in the vascular involvement stage and granulomatous inflammation in the gummatous stage. In primary syphilis, rate ridges are widened and elongated with epidermis hyperplasia (74). Once ulcerated, infection site is covered with an exudate rich in polymorphonuclear leukocytes, necrotic tissue fragments, and fibrin. Adjacent dermis is infiltrated densely with inflammatory cells including lymphocytes, plasma cells, polymorphonuclear cells and histiocytes. Swelling of endothelial cells can be observed in perivascular area in primary syphilis. Colonization of *T. pallidum* can be seen dermal-epidermal junction in the perivascular area at this stage (205).

Secondary syphilitic lesions exhibit complex histological changes. Almost every patient (75-100%) affected with secondary stage of the infection show dermis infiltrated of dense populations of lymphocytes and plasma cells. These infiltrates may progress in to granulomatous lesions. Endothelial swelling is spread to small blood vessels. Epithelial cells in the epidermis exhibits a variety of changes including acanthosis, exocytosis, spongiosis, and parakeratosis, Treponemes are present up to 70% affected individuals at this stage (2, 74).

T. pallidum possess several interesting mechanisms of immune evasion. In particular, treponemes maintain few organisms in distant anatomical sites during the episode of infection and even lesser numbers in the latent stages attributed to their slow rate of cell division, As a consequence, bacteria manage to maintain antigenic masses lower than the "critical" is required to trigger a host response (35, 168). as late latent syphilis must be treated by a prolonged course of penicillin to prevent treatment failure (1, 250). Nonetheless, detailed genetic, histopathological and clinical data derived from infected human tissues are essential to unravel physiological, pathological and biochemical function and processes of *T. pallidum.* Such knowledge, in turn, is likely to yield better insight into the pathogenesis of syphilis and facilitate generating novel therapeutic targets.

Clinical presentation

Syphilis has an incubation period of 10–90 days (average 3 weeks) and is characterized by four main clinical stages: primary, secondary, tertiary, and late or quaternary (192).

Primary syphilis

After 3-4 weeks of incubation period, a primary chancre develops at the site of entry. This is usually on genetic mucosae but may be seen in the mouth or oropharynx. A chancre is a flat, red, indurated, painless, highly infectious ulcer with a clean base and a serous exudate. Ulcers are marginated with surrounding tissue edema and 0.3-3cm in diameter. However, clinical and research reports have indicated that the morphologic presentation of chancre could exhibit significant variability, making clinical diagnosis unreliable (42, 44, 175). The ulcerations can be single or multiple and last for about 2-8 weeks and regress spontaneously. About 7–10 days after the development of the genital chancre, 80% of cases develop regional lymphadenopathy which are firm, painless and discrete with a rubbery consistency on examination (63, 102, 196, 231).

<u>Oral manifestations</u>

Though the chancre primarily appears on the genitalia, extragenital primary lesions occur in about 4 -12% of patients with syphilis (30, 128, 202). Approximately 40–75% of extragenital chancres occur in the oral cavity; especially in the tongue, gingiva, soft palate and lips (82). A chancre of the lips is the most common extragenital orofacial site (60% of cases, Figure 4). Chancres in the upper lip are common in men whereas the lower lip is more commonly involved

in women (192). In contrast to painless extraoral lesions, intraoral chancres are usually slightly painful due to secondary bacterial infections, as are the enlarged lymph nodes in the submaxillary, submental and cervical regions. Lesions are usually single and highly infectious (30, 128, 202).

The differential diagnosis of primary syphilis includes ruptured vesicles of herpes simplex, traumatic ulcers and carcinoma (192).

Secondary syphilis

Secondary syphilis develops after 2-12 weeks of first contact and two months after healing of primary syphilis. However, it is not unusual to observe lack of demarcation between these two stages as about one-third of patients with secondary syphilis may have primary chancre present at the same time (43, 149, 169). Secondary infection is due to haematogenous dissemination of the pathogen and results in constitutional and mucocutaneous manifestations. The signs of secondary syphilis can vary among individuals and depend on the organs affected. A skin rash with symmetrical 3–10 mm pink or red macules, papules or pustules are the frequently presenting clinical feature (75% of cases) and can be located on arms, palms, flanks and soles of feet (20, 63, 102, 196, 231). Minor proportion of the infected population have experienced varying degree of pruritic, though these rashes are generally known to be non-pruritic (43). These lesions usually heal within several weeks if left untreated and may result scarring, hyper or hypo-pigmentation. When scalp is involved, a classic "moth-eaten" appearance can be observed as a result of alopecia in up to 7% of affected individuals. Other symptoms include multiple mucous patches (33% of cases), generalized lymphadenopathy (50% of cases), condyloma latum in intertriginous areas, and ocular involvement such as uveitis, iritis, optic neuritis, joint involvement (arthritis, periostitis) glomerulonephritis and neurological involvement. Systemic symptoms are 'influenza like', and include fever, headache, weight loss, malaise and general aches and pains (82, 192).

<u>Oral manifestations</u>

The classic oral lesions are slightly raised, greyish white, glistening multiple mucosal patches on the tonsil, soft palate, tongue, and buccal mucosa : gingival tissues are more rarely affected (30, 63, 202). The surface of these lesions is covered with a greyish membrane which can be easily removed and contains many spirochetes (82, 192). When multiple mucous patches become confluent, characteristic `snail tracks` and mucous patches can result and are seen in about a third of those affected (figure 5). Nonspecific pharyngitis, tonsillitis and laryngitis are often associated with secondary syphilis and lesions on the larynx and pharynx may cause hoarseness (30, 114, 163, 202, 241). Similar to the primary chancre, these lesions are also highly infectious and heal spontaneously in two to six weeks.

The differential diagnosis of secondary syphilis includes aphthous ulcers, erythema multiforme, lichen planus and tonsillitis (192).

Tertiary syphilis

Tertiary syphilis is rarely seen today due to advancement of disease control. However, if left untreated, one third of cases could develop tertiary syphilis at any time from two to three years after the primary infection (102, 196, 231). Gummata, the classical lesion in tertiary syphilis, develope in skin, CNS, liver, spleen, bones and other organs (102, 196, 231). These lesions range from a pinhead size to several centimeters in diameter. They can present as solitary or multiple lesions and are non-infective as the tissue damage is due to a Type IV delayed hypersensitivity reaction (192).

<u>Oral manifestations</u>

Gummata are usually isolated to the hard plate, however, the soft palate, lips, tongue and face are also relatively commonly involved (82, 192).The lesion initiates as a small, pale, raised area and rapidly developes to an ulcer which progresses to a large zone of necrosis. The process could denude underlying bone, and palatal lesions may eventually perforate into the nasal cavity (192). The midline of the plate is usually affected, and the involvement of soft palate is rare. The lesions are painless and have low infectivity (192).

In rare cases, syphilis can affect the mandible and maxilla in the form of osteomyelitis. The condition resembles pyogenic osteomyelitis both clinically and radiologically with symptoms of pain, swelling, suppuration and sequestration (192). Atrophic/ interstitial glossitis can also be resulted by tertiary syphilis. Atrophy of the filiform and fungiform papillae exposes the tongue to many noxious stimuli and leukoplakia frequently develops. However, the relationship between tertiary syphilis and carcinogenic potential is yet to be determined (192). Secondary and tertiary syphilis have been reported in salivary glands (192).

Congenital syphilis
Treponema pallidum is capable of crossing the placental barrier. Consequently, the fetus can be infected during the second or third trimester from a mother either in the primary or secondary stage of syphilis (192). If left untreated, syphilis during pregnancy can lead to profound undesirable outcomes including spontaneous abortion, premature delivery, stillbirth, or perinatal death (85, 108, 177, 233, 244, 245). For up to 40% of infants have been reported to be born to untreated syphilitic mothers prematurely and with low birth weights (109, 117).

Oral manifestations
Infection of the developing tooth germ by *T. pallidum* can result in various dental anomalies. Deciduous teeth are minimally affected. Infection of the developing permanent tooth germ results in either the complete failure of development or a malformation. Early orofacial manifestations of congenital syphilis include periostitis (frontal bossing of Parrot), diffuse maculopapular rash, and rhinitis. Late manifestations such as dental anomalies, sensorineural hearing loss, and interstitial keratitis of the cornea, may appear at least 24 months after birth (192).

The common dental manifestations include small, hypoplastic first permanent molar teeth with poorly developed cusps ('mulberry molar' teeth) and the upper central incisors with crescentic notches in the middle of incisal edge (Hutchinson's incisors). Due to their calcification process during the first year of the infant's life, mainly the permanent incisors and first molars are affected by congenital syphilis (128). Lower incisors are less affected. Infection of the developing bones of the face may lead to open bite and a 'dished' appearance to the face (192). Atrophic glossitis, a high and narrow palatal vault and (Parrot's) radial scars—rhagades—of the lips are less common manifestations (192).

Laboratory diagnosis
Dark-Field Microscopy and direct fluorescence using a fluorescin-labeled antitreponeme serum is often used to identify the pathogen from the primary and secondary lesions (53, 118, 181, 196, 231). However, both dark-field microscopy and direct fluorescent antibody testing carry limited value in distinguishing *T. pallidum* from the other pathogenic Treponemes (103, 181).

Serological tests for syphilis can be either nontreponemal tests for screening, or treponemal tests for confirmation (118, 181, 196). The nonspecific nontreponemal reaginic antibody tests such as VDRL (Venereal Diseases Reference Laboratory) test, Rapid plasma reagin (RPR) test and microhemagglutination assay (MHA-TP) are inexpensive, rapid, and convenient for screening a large number of sera (82). Nontreponemal tests detect an anti-cardiolipin antibody present in the syphilitic patients' sera using an antigen comprising lecithin, cholesterol, and purified cardiolipin. These antibodies can be used to monitor the efficacy of antimicrobial therapy (192). However,

non-treponemal tests are known to possess less sensitivity in early and late syphilis with higher ratio of false-positive reactions. False positive reactions are more prominent with increased age, pregnancy, malignancy, drug addiction, and autoimmune diseases (e.g. systemic lupus erythematosus) and viral, protozoal, or mycoplasmal infection (109, 125, 181, 213).The treponemal tests are considered most sensitive and specific (181, 196). These tests include *T. pallidum* haemagglutination test (TPHA), fluorescent treponemal antibody-absorption test (FTA-Abs), which detects both IgM and IgG antibody, and ELISA (192). With recent advances in diagnostics, PCR and multiplex PCR have been applied in identifying *T. pallidum* DNA and known to possess very high sensitivity, and becoming increasingly popular in routine clinical use (103).

Despite the diagnosis of syphilis is based on clinical presentation and serological findings, in rare cases such as oral lesions and unusual presentations in HIV positive patients, histopathological examinations can be used to confirm the diagnosis (18, 50, 97, 196, 231). These reveal a characteristic histopathological picture such as focal collections of plasma cells, angiogenesis, dilation and thickening of blood vessels, mural oedema and large endothelial cells, perivascular infiltration of plasma cells in secondary syphilis; vasculitis, fibrinoid materials with necrosis in malignant syphilis.

Treatment

The drug of choice for all forms of syphilis is procaine benzylpenicillin. Doxycycline, tetracycline or erythromycin can be effective for patients hypersensitive to penicillin. Follow-up with regular clinical and serological examinations is necessary for at least two years and, contact tracing is recommended (82, 192, 230, 231). The type, dose and the duration of the antibiotic treatment is determined by the stage of syphilis. Factors such as the degree of spirocheticidal action, variability in absorption, level of patient compliance and individual circumstances such as pregnancy must also be considered when determining the choice of antibiotic (165, 185). Some studies have shown that there is a likely potential of *T. pallidum* to develop antibiotic resistance, however, there are no follow-up studies conducted or measurable penicillin resistance reported so far (165, 212).

Tuberculosis

Incidence

Tuberculosis (TB) is caused by various strains of mycobacteria, usually *Mycobacterium Tuberculosis* in humans (61). According to the World Health Organization (WHO) report in 2013, nearly 8.6 million people worldwide became infected with TB. There were around 1.3 million TB-related deaths worldwide in 2013 (112).

Oral lesions due to tuberculosis are extremely rare and seen in only 0.1-5% of all TB infections (112). They may be due to secondary inoculation with infected sputum or arise from haematogenous spread. Recent outbreaks of extra pulmonary infections of TB are reported due to the emergence of drug-resistant TB and AIDS (acquired immune-deficiency syndrome) (17, 120).

Predisposing factors

Crowded urban living, poor health and hygiene, poverty, drug abuse, HIV/AIDS and immunosuppression are established predisposing factors for the development of TB (249). In addition, local factors such as poor oral hygiene, local trauma and irritation, may facilitate the pathogen to invade oral mucosa (71, 110, 170).

Pathogenesis

Alveolar macrophages express various surface receptors such as C-type lectin receptors (e.g. macrophage mannose receptors), scavenger receptors (e.g. Class A and B Scavenger receptors),

and complement receptors (e.g. Compliment receptor 3) to bind and ingest, *M. tuberculosis* when first inhaled and reach the distal alveoli (200). Although studying mycobacteria and receptor interactions is difficult due to the complexity of uptake mechanisms, it is believed that the intracellular fate of ingested bacteria depends on the specific receptor (11, 116, 172). Despite most studies on mycobacterial entry have been conducted on alveolar macrophages, the other phagocytic cells such as neutrophils, monocyte-derived macrophages, and dendritic cells within alveoli also capable of ingesting mycobacteria (173). It is long believed that once being ingested, *M. tuberculosis* prevents maturation of the phagosome to reside long term in it ("intracellular bacterial trafficking") using various mycobacterial lipid and protein effectors (172). The arrest of phagosome maturation allows the mycobacteria to prevent developing intra-phagosomal acidic, degradative environment as well as to acquire nutrients by recycling endosomes (189). Recent findings suggested that the bacterium can even continue to grow and proliferate within the immature phagosome (144, 237, 242). As a consequence of complex interactions between the intracellular mycobacteria and the host cells, the latter undergo necrosis or apoptosis. Necrotic macrophages containing mycobacteria trigger recruitment new macrophages and initiate granuloma formation (57). The necrotic cells are rapidly ingested by newly recruited macrophages allowing remaining mycobacteria to further expand the population (81, 86 phillips). Importantly, a fraction of infected macrophages departs from the early granuloma to initiate infection at distant sites (47, 56).

Oral manifestations

Oral TB can be present as ulcers, tuberculomas, nodules, (72, 170, 203) and commonly affects the tongue. Other frequently affected sites include the palate, lips, buccal mucosa, gingiva, palatine tonsil, uvula, floor of the mouth and salivary glands (72). Occasionally, a periapical granuloma may develop as a result of TB.

Primary oral TB lesions are rare, and usually affects young adults. The lesion typically present as a single painless ulcer associated with enlarged regional lymph nodes. Most commonly these lesions are secondary to pulmonary disease. These lesions appear as single, indurated, irregular, painful ulcers covered by inflammatory exudates. Classically, tuberculous ulcers of the tongue are pale, irregular, and indolent with inverted margins and granulations on the floor with sloughing tissue and are often misdiagnosed as malignant ulcers (145). Though individuals in any age group may be affected, the disease is more common in the middle-aged and elderly. Medically compromised individuals such as those with HIV disease may exhibit TB at younger ages (112, 146, 170).

Diagnosis

Diagnosis of TB is often made with history, clinical examination, chest x-ray and sputum cultures and histopathology for detection of acid fast bacilli. Oral tuberculosis lesions can be diagnosed in biopsies for the presence of acid fast mycobacterium using Zeihl- Neelsen stain. Fine-needle aspiration cytology is indicated for identifying TB in the major salivary glands (75, 112).

Treatment

The management of oral manifestations of TB must be coordinated in liaison with a respiratory physician and a full work up of the patients is necessary. Current regimen of anti-TB therapy is based on daily administration of combination of four drugs (isoniazid, rifampicin, pyrazynamide, and ethambutol) for the first two months, followed by a course of two drugs (isoniazid and rifampicin) for additional four months (203). World Health Organization (WHO) launched directly observed therapy short course (DOTS) in 1997 due to the complexity of the traditional TB management regimen (112).

Drug resistance of *M. tuberculosis* is a global issue of major concern. Approximately 580, 000 multidrug resistant cases have been estimated in 2015 (209). Multidrug resistant TB exhibit resistance to first line anti-TB medications (isoniazid and rifampicin) while extensively resistant-

TB is resistant to both first line and second line agents (aminoglycosides and/or cyclic polypeptides-capreomycin, kanamycin and amikacin) and fluoroquinolones. Fifty percent of reported multidrug resistant TB patients showed resistance to a fluoroquinolone, to a second-line injectable drug, or both (209). Novel drugs such as nitroimadazoles, diarylquinolines, oxazolidinones have been recently introduced to overcome both multidrug and extensively resistant TB (112).

Precautions must be taken by the dental health practitioners when treating patients with TB. Thorough medical history must be taken, and only essential treatments should be provided for those with active TB. Usage of routine barrier protection to prevent contact with blood, body fluids and mucous membranes of the patient, with standard infection control protocols and an appropriately equipped room with effective air evacuation are recommended (112).

The oral cavity may manifest many other rare bacterial infections. Please refer to Table 2 for further information.

Fungal infections

Fungi are a large, complex group of eukaryotes, increasingly recognized as emerging pathogens. The traditional thinking was that *Candida* species were the major eukaryote present in the oral cavity. However, the arrival of new methodology such as pyrosequencing and new generation sequencing (NGS) techniques have revolutionized the traditional views and has revealed a novel oral mycobiome hitherto unimagined (68).

For instance, recent data indicate a high prevalence and abundance of the genus *Malassezia* an important pathogen of the skin, in the healthy human oral cavity. Despite these findings, Candida infections remain as the predominant fungal infections that are seen by dentists. It is noteworthy however that rare fungal diseases caused by species such as Histoplasma, Geotrichum, Penicillium and Aspergillus species, essentially seen in compromised population groups, are not discussed below.

Candidiasis

Epidemiology

Oral candidiasis is the most common human fungal infection (3, 4, 88). It is estimated that approximately 5-7% of infants less than one month old , and 9-31% of AIDS patients, 65% of denture wearers and nearly 20% of cancer patients develop oral candidiasis (4, 36). *Candida* carriage in the oral cavities of general population is reported to be between 20% - 75% (88). In particular, 45% of neonates, 45-64% of healthy children, 30-45% healthy adults, 50-65% of those who wear removable dentures, 65-88% in the individuals in acute and long term care facilities, 90% of patients under chemotherapy for acute leukaemia and 95% of patients with HIV carry *Candida albicans* in their mouth (5, 10, 23, 28, 52, 67, 99, 133, 140, 186).

Predisposing factors

Similar to many other opportunistic infections, Candidiasis generally occurs in immunocompromised patients. Oral candidiasis is usually seen in patients with impaired salivary gland functions, drugs (Steroid inhalers, psychotropic drugs, immunosuppressives and broad spectrum antimicrobial therapy), denture wearing, high carbohydrate diets, age (infants and older geriatric populations), smoking, diabetes, malignancies, Cushing's syndrome, HIV/AIDS and other immune deficient conditions (4).In essence oral candidiasis is a disease of the `very young, the very sick and the very old.

Pathogenesis

Candida spp. possess a wide variety of virulence attributes to facilitate its colonization and causation of superficial and/or deep seated systemic infections. Like most other microbial

pathogens, the key to infect the host by *Candida* is its successful colonization of within the host tissues. In susceptible individuals, *Candida* attach the epithelial surfaces and acquire nutrients from the host to generate pathogenic colonies. This process of colonization is mediated by an array of *Candida* virulent factors which include adhesins, hydrolytic enzymes, formation of hyphae, phenotypic switching and molecular mimicry (33, 156). Adhesins, arguably one of the most vital virulent determinant of *Candida*, are specialized set of proteins that facilitate the fungus to adhere to both biotic and abiotic surfaces. Among these adhesins, agglutinin-like sequence (ALS) proteins (143, 153, 171, 256), morphology associated proteins (e.g. hyphal wall protein; Hwp1), morphology-independent proteins. These include GPI-linked proteins (Eap1, Iff4 and Ecm33), cell-surface associated proteases (Secreted aspartyl proteinases: Sap9 and Sap10), non-covalent wall-associated proteins (putative β-glucanase: Mp65, and β-1,3 glucanosyl transferase: Phr1), and the integrin-like surface protein (Int1) have been shown to mediate *Candida* adhesion (157, 254). Despite the existence and the role of extracellular proteinases of most dimorphic human pathogenic fungi are yet to be fully elucidated, the proteolytic system of *C. albicans* is well understood (58, 87, 106, 107). Recent studies suggested that non-*albicans Candida* species such *as Candida dubliniensis* (92), *Candida tropicalis* (150, 228, 253), and *Candida parapsilosis* (60, 150), also possess the machinery of synthesis of Secreted aspartyl proteinases (Sap), major class of extracellular secreted by *C. albicans.* Interestingly, Sap production is interlinked with other *Candida* virulence attributes such as adhesion (Sap 9 and 10, hyphal formation, and phenotypic switching. The precise role of secretory proteinases during human infections is yet to be fully established (156). While morphological switching such as formation of hyphae is well-known to assist *Candida* attachment, the role of white opaque switching is yet to be fully unraveled.

Unlike most other pathogens, *Candida* utilizes more than a single mechanism of tissue invasion i.e. induced endocytosis and active penetration (54, 157, 252, 254). During induced endocytosis, *Candida* binds to host ligands such as E-cadherin on epithelial cells and N-cadherin on endothelial cells using invasins, a group of specialized cell surface proteins (171). Fungal invasin-host ligand interaction triggers host cell mechanisms of fungal engulfment. *Candida* Als3 and Ssa1 have been identified as two major cell surface invasins that induce endocytosis (171, 222). Interestingly the viability of the yeast or the morphological status do not play a critical role during engulfment (54, 166). In contrary, only viable Candida is capable of penetrating host tissues and hyphae plays an essential role in active penetration. Despite a little is known on the driving factors of invasion of epithelium by hyphae, latest evidence suggests that fungal adhesion and physical forces, Sap proteins but not lipases and phospholipases may mediate active penetration (54, 157, 240). Once invaded, *Candida* continue to degrade host proteins using hydrolytic enzymes and establishes a superficial candidiasis (157). In some cases, *Candida* continues to penetrate tissues and blood vessels to develop deep seated infections. There are many mechanisms described in relation to immune evasion of *Candida*, particularly using immune modulators and host mimicry and are beyond the scope of this review. Deep seated infections, with continuing host immune suppression, such as in HIV and malignancies, may lead to disseminated infections. In such events, *Candida* are capable of adhering to endothelial cells, infect distant organs and trigger coagulation cascades resulting serious complications to host (156, 157).

Clinical features

Oral candidal infections can be essentially sub-divided into three groups as pseudomembranous, erythematous and hyperplastic variants, as discussed below. There are also a number of other conditions such as *Candida* associated denture stomatitis, angular cheilitis and median rhomboid glossitis and the newly described entity, linear gingival erythema which ae mulltifactorial in nature and not necessarily associated with candidal infections. In clinical terms these lesions do not often resolve by antifungal therapy and there may be other underlying reasons for the disease condition.

Pseudomembranous candidiasis (Thrush)

Oral thrush characteristically appears as extensive white plaque like pseudo membranes that can be easily wiped off to expose underlying erythematous mucosa. The lesions are commonly seen at labial and buccal mucosae, tongue, hard and soft palate, periodontal tissues and oropharynx (Figure 6). One third of oropharyngeal candidiasis is reported to be of pseudomembranous type (4, 191).

Erythematous (atrophic) candidiasis
This is often asymptomatic but in some cases the principal complaint is burning sensation of the oral mucosa, particularly the tongue (Figure 7). The latter appears to be bright red and sometimes de-papillated due to loss of filiform papillae (160). The appearance of the tongue mimics the manifestations of the tongue in serum B12, folate or ferritin deficiencies. 'Antibiotic sore mouth' is commonly associated with usage of broad spectrum antibiotics or steroid inhalers (4, 70, 211).

Chronic hyperplastic candidiasis
Well demarcated, slightly elevated and adherent, nodular, speckled or homogenous white or translucent lesions occur characteristically on the buccal mucosa or lateral border of the tongue (77, 206) (Figure 8). Unlike the pseudomembranous variant, these lesions cannot be wiped off (206). The lesions may progress in to severe dysplasia or malignancy thus refers as candidal leukoplakia. However, the association of *Candida* and the malignant potential is still questionable (64). There is a known association between chronic hyperplastic candidiasis and smoking (204).

Candida Associated Lesions

Candida-Associated denture stomatitis
Previously known as chronic atrophic candidiasis this condition is perhaps the most common fungal infection in denture wearing elderly These lesions can commonly be seen as an erythematous and oedematous area in the palatal denture bearing mucosa, and less commonly on the mandibular mucosa (160). The denture stomatitis is usually asymptomatic; however, mild soreness or burning sensations may occur in some cases. Depending on the severity, denture stomatitis is further classified in to three groups; type I (localized, simple pin point inflammation or erythema, Figure 9), type II (diffuse, erythematous lesions covering a part or entire denture bearing area, Figure 10) and type III (granular or papillary lesions appearing on the alveolar ridge or in the middle of the palatal mucosa, Figure 11) (194).

Median rhomboid glossitis
Median rhomboid glossitis which is also known as central papillary atrophy is a variant of erythematous candidiasis (159). Lesions are well demarcated, erythematous, elliptical or rhomboidal area of papillary atrophy in the dorsum of the posterior tongue in front of the circumvallate papillae (182) (Figure 12). In some patients, palate also can be affected and is also called 'kissing lesions'. Kissing lesions are resulted due to direct candidal inoculation to the palate from the lesions in the dorsal tongue. Hence, this often called chronic multifocal candidiasis (160).

Angular Cheilitis
Angular cheilitis is characterised by erythema, crusting and fissuring and maceration (Figure 13). These chronic inflammatory lesions can be exclusively seen in the labial commissures and often isolated bilaterally (182). Angular cheilitis is often seen in older population due to accentuated skin folds as well as due to reduced occlusal vertical dimension which result pooling of saliva providing an optimal growth conditions for *Candida*. In addition, lip sucking, nutritional deficiencies such as iron, Vitamin B and high carbohydrate diets are associated with the pathogenesis of angular cheilitis (160). Angular cheilitis is strongly associated with mixed infections of *Candida* and *Staphylococcus spp.* (247).

Linear gingival erythema
This condition, defined as a localized or generalized erythe-matous band extending along the gingival margins (between adjacent gingival papillae), was first described in HIV-infected individuals; it is however not confined to the latter group. Although *Candida* are implicated in the pathogenesis, and lesions resolve after antifungal therapy in some cases, it is likely that other cofactors such as oral hygiene play an equally important role.

Candidiasis and immunocompromised hosts
A few patients have chronic candidiasis from an early age, sometimes with a definable immune defect, e.g. chronic muco-cutaneous candidiasis. Candidal infections in these patients are seen in the oral mucosa, skin and other body parts. These secondary oral candidal infections have increased recently because of the high prevalence of attenuated immune response, consequent to diseases such as HIV infection, haematological malignancy and treatment protocols, including aggressive cytotoxic therapy.

Oral candidiasis in HIV disease
Candidal infections, with oral thrush and oesophagitis as frequent clinical manifestations, are the most common opportunistic infections encountered in acquired immune deficiency syndrome (AIDS). It has also been shown that the occurrence of an otherwise unexpected mycosis (typically oral candidiasis) in an HIV-infected individual is a poor prognostic indicator of the subsequent development of full-blown AIDS. However, in HIV-infected populations on antiretroviral therapy, the incidence of oral candidiasis has significantly declined.

Diagnosis of oral candidiasis
Diagnosis of oral candidiasis is often made with a thorough history and the clinical presentation. Some laboratory investigations can also be used as adjuncts to confirm the clinical presentation. *Candida* pathogens in a smear taken directly from the lesion are commonly identified using Gram staining or periodic acid Schiff (PAS) staining, or by culturing the pathogen in Sabaraud's dextrose agar (SDA) (89, 193). Biopsies are useful in identifying the organisms and hyphae together with histopathological changes in chronic hyperplastic candidiasis (121).

Treatment
Treatment of oral candidiasis is primarily based on the identification of underlying predisposing factors and correcting them. Nutritional deficiencies, broad spectrum antibiotics and inhalational steroids usage, diabetes mellitus, poor oral and denture hygiene, ill-fitting dentures, salivary disorders need to be identified and corrected. When the predisposing factors cannot be corrected, antifungal agents are indicated (77, 78). The choice of the antifungal agent is based on the clinical presentation and the medical history of the patient. Most oral candidiasis can successfully be treated with topical azoles or polyenes.

Effective topical dosage of nystatin include oral suspensions (100,000units/mL, 1mL topically), or pastilles (100,000IU, four times daily for 1-2 weeks) (78). Recommended Amphotericin dosage for oral candidiasis include lozenges (10 mg) or suspension (100mg/mL) four times daily for 2-3 weeks (77). Topical application of miconazole 2% gel, four times daily for 2-3 weeks is also effective against oral *Candida* infections. For refractory and recurrent oral candidiasis, systemic antifungals such as ketoconazole, fluconazole and itraconazole and amphotericin may be indicated (78). The inability of most antifungals to penetrate robust *Candida* biofilms have resulted an ongoing challenge for both clinicians and researchers when determining an efficient and appropriate management strategy in eliminating *Candida* infections. Particularly, efficient, low side effect carrying antifungals such as fluconazole are known to fail in eradicating *Candida* biofilms (34, 174). Consequently, in recent years, studied have been conducted in identifying

novel treatment options such as usage of probiotics, plant derivatives, and photo dynamic therapy for managing mucosal candidiasis (26, 141, 142, 232). While *in vitro* laboratory findings of these studies are promising, in detailed clinical evidence are necessary prior to implementing such treatment strategies.

In addition to candidiasis, several other mycoses also cause characteristic oral lesions. The reader is referred to table 3 for these rare important fungal infections that may manifest in the oral cavity.

Concluding remarks and future perspectives

Global pandemics are still a major concern in health care and economic set ups and emergence and re-emergence of infections is not a new phenomenon. Despite consistent uplift of primary health care, serious infections such as HIV, TB still kill millions of individuals worldwide. Factors such as ever-increasing voyage frequencies of world population, environmental damage and natural disasters, overcrowding and poor sanitation, human-animal interactions, and rising sexual promiscuity will continue to challenge human body with a plethora of hitherto characterized and new microbial pathogens which will result new or re-emergence of localized and/or general infections

The early detection of the infection and identification of the pathogen is quintessential in mitigating oral and/or general infections in humans and animals. When determining the management of these infections, multifaceted approaches must be followed in identifying all aspects that confer antimicrobial resistance, immune evasion profiles, potential mutations and genotypic disparities must be followed (210). Timely management not only benefits patient by preventing/limiting complications but also benefits public by ceasing infection spread.

Improved continuous epidemiological surveillance (e.g. computer modelling of emerging infections (126)) together with early detection and management of infectious diseases is the foundation for successful strategies in controlling and eliminating oral and non-oral diseases. Emerging novel technologies that are currently under conceptual and optimising and launching stages as well as existing technologies that are being progressively improved is likely to assist infection management team to identify and treat infectious diseases. Various enzyme-linked immunoassays such as fluorescence polarization, micro-particle enzyme and chemiluminescent immunoassays are still widely used and being consistently undergoing improvements to identify those organisms emerge with various mutations while recently developed methods such as next generation sequencing provides extremely high sensitivity and specificity, quick results, lower detection limits, automation requiring smaller sample volumes. However, implementation such techniques for routine practices remain unrealistic due to lack of funding, resources and technical expertise. However, ongoing investigations of using microfluidic technologies such as microchips (e.g. lab-on-a-chip) (7, 210) to facilitate diagnosis in regional, resource and space limited settings appeared to be promising in future infection diagnostic paradigms.

The importance of proper training of oral and general clinicians and diagnostic microbiologists in all aspects of the management of infections of interest must be routinely conducted. For instance, oral clinicians need to be equipped with up-to-date knowledge of the clinical pictures of new infections, approaches in accurate identification of orally limited infections vs oral manifestations of underlying systemic diseases. Management protocols of complicated infections such as those manifesting other extra-oral involvement or when they are immunocompromised must be determined by a multidisciplinary team including oral clinicians, medical/surgical practitioners, microbiologists/pathologists as well as other case-specific specialities. Such tantalizing approaches will not only provide personalized and superior care for the patient but also directly impact, medical, social and economic outcomes worldwide.

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