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Sexually Transmitted Diseases: An Overview

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Introduction

Sexually transmitted infections (STIs) spread predominantly by sexual contact, including vaginal, anal and oral sex. Some STIs can also be transmitted from mother to child during pregnancy, childbirth and breastfeeding. The World Health Organisation (WHO) report reveals that more than 30 different bacteria, viruses and parasites are known to be transmitted through sexual contact. Eight of these pathogens are linked to the greatest burden of sexually transmitted disease (STD). Of these STIs, bacterial infections such as syphilis, gonorrhoea, chlamydia and trichomoniasis, a protozoal infection, are currently curable, whereas viral infections such as herpes simplex virus (HSV), human immunodeficiency virus (HIV), human papilloma virus (HPV) and hepatitis B virus infections are incurable [1].

Diagnosis of STIs requires a detailed history, thorough clinical examination, and appropriate investigations. Since many STIs are asymptomatic, screening for common STIs in at-risk populations, regardless of symptoms, is important for STI control and to prevent onward transmission.

Bacterial STIs

Syphilis

Syphilis is an STI caused by the spirochete bacterium, *Treponema pallidum*. The spirochete is transmitted by direct contact with an infectious lesion, gaining access through microabrasions in the skin during vaginal, anal and oral sex. Syphilis earned the name of 'the great imitator' due to its vast array of clinical presentations, including many oral manifestations, which may mimic other conditions. The infection progresses through clinical stages,

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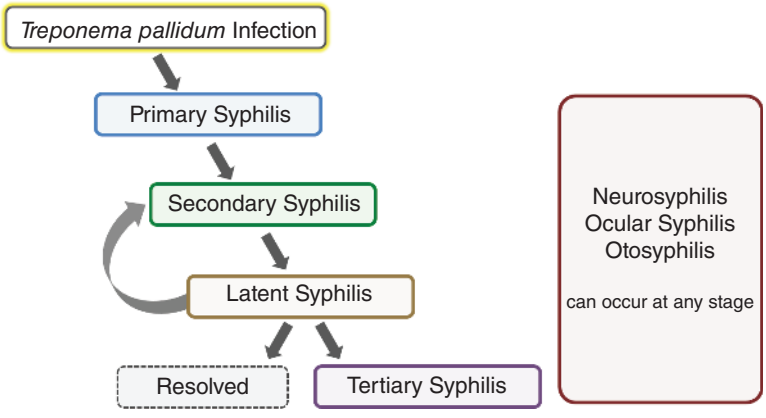

Figure 1.1 Natural history and clinical staging of syphilis. Source: Reproduced with permission from Spach and Mirchandani [2].

known as primary, secondary, latent and tertiary syphilis (Figure 1.1) [2]. The primary, secondary and tertiary phases have all been associated with oral lesions. It is therefore prudent for oral health practitioners to be familiar with the natural history of this infection and its associated oral manifestations.

Epidemiology

Syphilis continues to cause morbidity and mortality worldwide. WHO estimates that 7.1 million new cases of syphilis occurred among adolescents and adults aged 15–49 years worldwide in 2020 [1, 3].

Bacteriology, Risk Factors and Transmission

The etiologic agent in syphilis is *T. pallidum*. *Treponema* belongs to the spirochete class and is a corkscrew-shaped, motile microaerophilic bacterium that requires a live rabbit-model system for culture and cannot be viewed by normal light microscopy. This spirochete bacterium is thin (0.1–0.18 μm in diameter) and 6–20 μm in length with typical corkscrew motion on dark-field microscopy (Figure 1.2) [2, 4].

The major routes of transmission for *T. pallidum* are sexual (during the primary and secondary stages of syphilis) and haematogenous (in utero via transplacental spread to a foetus) [2, 5]. During sexual transmission, *T. pallidum* enters the body via breaches in skin and mucous membranes. Although sexual transmission of *T. pallidum* usually results from contact at genital mucous membranes, it can also occur at other body areas, including the mouth, anorectal areas and cutaneous lesions. Maternal transmission predominantly occurs via transplacental passage of *T. pallidum* during maternal spirochetemia; less often, transmission can occur if the newborn has contact with maternal genital lesions at the time of delivery [2, 5].

Clinical Features

Primary Syphilis

Primary syphilis occurs around the time of initial infection with *T. pallidum* when it penetrates the mucosa, forming an infectious lesion, the chancre, at the site of inoculation within 9–90 days. The lesion is typically a painless, but may be painful, firm, round

Figure 1.2 *Treponema pallidum*: dark-field microscopy. This photomicrograph shows the typical spiralled 'corkscrew' appearance of several *T. pallidum* spirochetes with the dark-field microscopy technique. Source: Renelle Woodall, 1969, Center for Disease Control (CDC) – PHIL/Public domain.

indurated ulcer lasting from approximately three to seven weeks, which heals without scarring. They may be single or multiple ulcers and occur on the genitalia or other sites of contact such as extra genital sites including the lips, tongue and oral mucosa (see Chapter 12). These lesions are highly infectious and may go unnoticed by the patient before they heal. Left untreated, the infection enters the second stage.

Secondary Syphilis

Within 10 weeks of inoculation, haematogenous and lymphatic spread of the spirochetes may result in clinical features of secondary syphilis, which can affect every system including the central nervous system. Patients with secondary syphilis may present with an array of non-specific features including fever, generalised lymphadenopathy and non-pruritic rash, typically affecting the palms of the hands and soles of the feet. Oral lesions occur in a third of cases of secondary syphilis and can be diverse and non-specific. These include pharyngitis, glistening plaques and oral ulcers [6] (see Chapter 12). The classical lesion, known as the mucous patch, is a shallow, irregular grey-white plaque with an erythematous base. They are usually bilateral, often involving the tongue and may extend to 1 cm in diameter. Snail track ulcers describe multiple mucous patches becoming confluent [6].

Latent Syphilis

Latent syphilis is a stage of syphilis characterised by the persistence of *T. pallidum* organisms in the body without causing signs or symptoms [2]. Clinical signs and symptoms of secondary syphilis may resolve spontaneously, and, if left untreated, the infection enters a latent phase. Patients with latent syphilis typically remain infectious for the first two years of infection, termed early latent, followed by late latent syphilis of variable duration which

is usually non-infectious. While some patients will remain in the latent phase, a third of patients undiagnosed and untreated will enter the tertiary phase, which may occur decades after the initial infection [7].

Tertiary Syphilis

Without treatment, approximately 30% of patients will progress to the tertiary stage at 2–50 years after the original infection [2, 7, 8]. Lesions of tertiary syphilis manifest as locally destructive granulomatous lesions with a necrotic central core affecting the skin, mucous membranes, neural tissue, bone and/or any visceral organ. Oral gummata are rare but may affect the tongue or palate and may range in size to more than 1 cm (see Chapter 12). Perforations of the nasal cavity or the maxillary sinus may complicate palatal gummata [9]. Tertiary syphilis can present as an interstitial glossitis where the tongue appears erythematous with a loss of surface papillae and can become fissured and lobulated [9]. If there is any suspicion of syphilis in a patient presenting for dental care, referral to a medical healthcare provider is necessary. Dental treatment should be deferred, and reasonable infectious disease precautions taken as syphilitic lesions in the first and second stages of disease are highly infectious.

Congenital Syphilis

T. pallidum can be transferred via the placenta from an infected mother to the developing foetus in utero. Untreated syphilis in pregnancy is associated with poor obstetric outcomes including foetal and neonatal death, and congenital syphilis [10, 11]. Clinical manifestations of congenital syphilis include perforation of the hard palate and Hutchinson's triad consisting of interstitial keratitis, vestibulocochlear nerve deafness and Hutchinson teeth. Developmental processes of enamel-forming cells are hindered by *T. pallidum* [12]. Later, formation of the crowns is disrupted, with characteristic semilunar notches on the incisal edges (Hutchinson teeth) [13] (see Chapter 12). Malformation of the enamel of permanent molars results in mulberry molars and doming of the first permanent molars causes Moon's molars. Congenital syphilis may also lead to premature loss of deciduous teeth with resultant delay in speech development and problems with eating [9]. If a child is suspected of having congenital syphilis, referral to a paediatrician with an interest in infectious disease is urgently required.

Diagnosis

Diagnosis of syphilis relies on detailed history, including a sexual history, clinical examination and laboratory investigations. As *T. pallidum* is too fragile for an organism to be cultured, diagnosis is made by direct visualisation of the organism or indirect evidence of infection. For primary chancres, dark ground or dark-field microscopy may be performed, in specialised centres, on exudate obtained from the lesion for direct visualisation of the spirochete. When this is not available, and for cases of secondary syphilis, where lesions are often dry, laboratory diagnosis relies on nucleic acid amplification testing (NAAT) of DNA extracted from infectious lesions and on serological testing of syphilis antibodies. Direct methods have the advantage, in some cases, of detecting infection before a patient has mounted a measurable antibody response that results in a reactive serology result. Serological tests are of two types: treponemal tests and non-treponemal tests. Treponemal tests include

syphilis enzyme immunoassay (EIA), *T. pallidum* haemagglutination (TPHA) or fluorescent treponema antibody (FTA) tests, which are specific for *T. pallidum*. FTA is the most sensitive test for detecting early disease. Treponemal serology remains reactive for life and cannot, therefore, be used to distinguish between new and past infections. Non-treponemal tests include Venereal Diseases Research Laboratory (VDRL) or rapid plasma reagin (RPR) which are non-specific cardiolipin antibody tests. Non-treponemal tests are used to identify reinfection or/and to monitor response to treatment. RPR and VDRL are reported as a 'titre'; a high titre is a marker of disease activity with titres reducing with successful treatment. False-positive test results can occur with non-treponemal tests due to other conditions such as hepatitis, infectious mononucleosis, collagen diseases (e.g. systemic lupus erythematosus), pregnancy or ageing. Gummata of tertiary syphilis are diagnosed by clinical evaluation including biopsy and demonstration of *T. pallidum* using silver staining. Patients with confirmed gumma should be screened for other complications of tertiary syphilis including neurosyphilis, ocular syphilis and cardiovascular complications.

Treatment

Penicillin G, administered parenterally, is the preferred drug for treating all stages of syphilis. The preparation(s) of penicillin used (e.g. benzathine, aqueous procaine or aqueous crystalline), the dosage and the length of treatment depend on the stage and clinical manifestations of the disease [2]. A single intramuscular injection of long-acting benzathine penicillin G (2.4 million units administered intramuscularly) will cure a person who has primary, secondary or early latent syphilis. Three doses of long-acting benzathine penicillin G (2.4 million units administered intramuscularly) at weekly intervals are recommended for individuals with late latent syphilis or latent syphilis of unknown duration [14]. Neurosyphilis as well as ocular and otosyphilis is treated with aqueous crystalline penicillin G 18–24 million units per day for 10–14 days (administered intravenously) [14].

Chlamydia

Chlamydia is an STI caused by the bacterium *Chlamydia trachomatis,* an obligate intracellular pathogen which depends entirely on the host cell's adenosine triphosphate for its energy [15]. The bacterium infects columnar epithelium at mucosal sites. Transmission of *C. trachomatis* occurs during ano-rectal sexual intercourse; however, transmission during oral sex and autoinoculation to cause conjunctivitis can occur.

Epidemiology

Chlamydia is the most prevalent bacterial STI in the world. Based on the STI surveillance from WHO, global estimation of new chlamydia cases in 2020 was 129 million [1, 3].

Aetiology/Risk Factors/Transmission

C. trachomatis is an obligate intracellular bacterium with a cell wall and ribosomes similar to those of Gram-negative organisms [16]. Sexually acquired *C. trachomatis* is highly transmissible with adolescents and young adults at increased risk for infection. Risk factors associated with acquisition of chlamydial infection include recent partner change,

multiple sexual partners, past history of STI and unprotected sexual intercourse. Transmission of *C. trachomatis* can also occur from mother to infant via the genital tract during birth [17].

Clinical Features

C. trachomatis causes a wide range of clinical manifestations and complications, including cervicitis, urethritis, pelvic inflammatory disease (PID), tubal infertility, pelvic pain and perihepatitis in women, and urethritis and epididymo-orchitis in men. Other manifestations in men and women may include conjunctivitis, oropharyngeal infection, proctitis/proctocolitis and reactive arthritis. Infants born to mothers with untreated *C. trachomatis* infection may develop conjunctivitis, pneumonia and urogenital infection [17]. Complications of such as epididymitis and epididymo-orchitis may result in men and PID from untreated ascending infection from the cervix in women. A different serovar of *C. trachomatis* can cause lymphogranuloma venereum, which presents as genital ulceration, lymphadenopathy and/or proctitis.

There are no specific oral manifestations of chlamydial infection, but asymptomatic infection of the throat occurs in those performing oral sex [18]. Oropharyngeal infection with *C. trachomatis* is most frequently asymptomatic in both men and women. It can also present as acute tonsillitis, acute pharyngitis or abnormal pharyngeal sensation syndrome (see Chapter 16). When clinical signs and symptoms are described, the presentation can range from minimally symptomatic disease (i.e. dry or pruritic throat) to exudative tonsillopharyngitis. Chlamydial tonsillopharyngitis is marked by generalised pharyngeal and tonsillar hyperaemia with possible addition of swollen anterior pillars and uvula, as well as diffuse purulent exudate on the tonsils [17].

Diagnosis

The *C. trachomatis* cell wall is unique in that it contains an outer lipopolysaccharide membrane but lacks peptidoglycan, meaning that conventional Gram staining is not useful in its detection. Diagnosis of *C. trachomatis* relies on nucleic acid amplification of DNA detected from anogenital or oropharyngeal specimens using NAAT. In most circumstances, the preferred diagnostic method for chlamydial infection is with a *C. trachomatis* NAAT, on urine samples, rectal and throat samples, clinician-collected endocervical and urethral samples, and self-collected vaginal swabs. Pharyngeal sampling is used to screen those who are at risk of asymptomatic throat infection [17]. The clinical significance of oropharyngeal *C. trachomatis* infection is unclear, and prevalence is low, even among populations at high risk. However, when gonorrhoea testing is performed at the oropharyngeal site, chlamydia test results might be reported because certain NAATs detect both bacteria from a single specimen.

Treatment

The recommended first-line treatment of chlamydial infections in non-pregnant women and all men is with a *doxycycline*, 100 mg twice daily, for seven days, with an alternative treatment option of single-dose *azithromycin* [14].

Gonorrhoea

Gonorrhoea is an STI caused by *Neisseria gonorrhoeae,* a Gram-negative bacterium that infects the columnar epithelium of the lower genital tract, rectum, pharynx and conjunctiva [15].

Epidemiology

In 2020, the WHO estimated the pooled global prevalence of urogenital gonorrhoea to be 0.8% in women and 0.7% in men, and in 2020, there were an estimated 82 million gonorrhoea cases worldwide [3].

Bacteriology, Pathogenesis and Transmission

N. gonorrhoeae is a Gram-negative kidney-bean-shaped coccus bacterium that is divided by binary fission and thus usually appears as pairs (diplococci) (Figure 1.3) [19]. The organism is able to attach itself to epithelial cells via several structures located on its surface, allowing it to infect mucosal surfaces, such as the urogenital epithelium, oropharyngeal tract and conjunctival tissue [20, 21]. It also has several virulence factors that facilitate immune evasion [20, 21]. Infection with *N. gonorrhoeae* generates limited immunity allowing repeated infections in an individual [22]

Transmission of *N. gonorrhoeae* can occur from the urethra in a person with gonorrhoea to the vagina or rectum, the vagina or rectum in a person with gonorrhoea to the urethra in a person without gonorrhoea, anogenital tract of a person with gonorrhoea to the pharynx of a person without gonorrhoea or via oral–genital or oral–anal contact; and from the pharynx of a person with gonorrhoea to the urethra of a person without gonorrhoea during fellatio [19]. Perinatal transmission (from mother to infant) can occur during vaginal delivery when a mother with gonorrhoea has not been treated during the perinatal period.

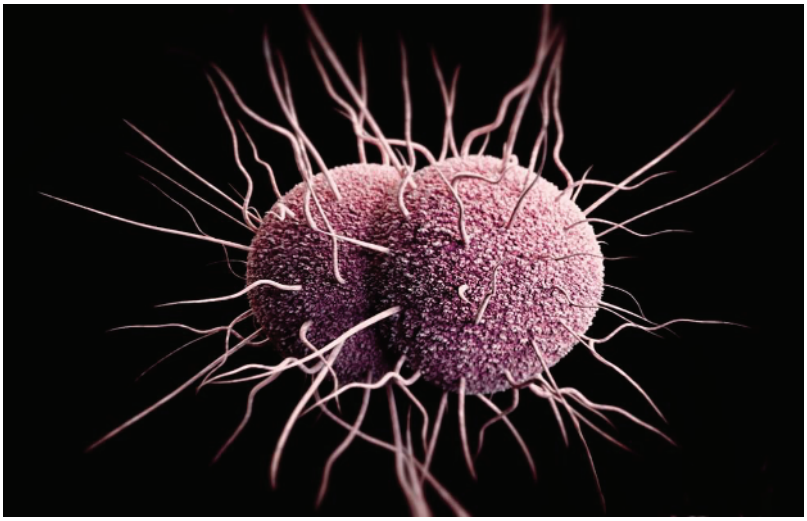

Figure 1.3 *Neisseria gonorrhoeae* [19]. Source: James Archer, 2013, Center for Disease Control (CDC) – PHIL/Public domain.

Clinical Features

N. gonorrhoeae infection may result in diverse clinical syndromes, including urethritis, cervicitis, pharyngitis, proctitis and conjunctivitis in adults and neonates. With an extension to the upper genital tract, it can cause pelvic inflammatory disease and epididymitis. Disseminated gonococcal infection (DGI) is rare and characterised by petechial or pustular acral skin lesions, asymmetric polyarthralgia, tenosynovitis or oligoarticular septic arthritis [14]. Infection of the throat results from oral–genital contact and most often results in asymptomatic infection. Symptomatic infection of the oropharynx is relatively rare, but when it occurs, patients may present with multiple ulcers, a fiery red appearance of the oral mucosa with a white pseudomembrane and associated lymphadenopathy (see Chapter 13). Oral manifestations of gonorrhoea are not specific, and may mimic other conditions affecting the oropharynx including symptomatic HSV infection, erythema multiforme and immunobullous disorders [6]. Despite the fact that infection rarely causes symptoms, the oropharynx remains an important site for transmission.

Diagnosis

Diagnosis of gonorrhoea infection involves careful history taking, clinical examination and laboratory diagnostic testing. In men, urethral infection with *N. gonorrhoea* typically presents as a purulent discharge, and the demonstration of the offending organism on Gram stain of the discharge (pink diplococci within polymorphonuclear lymphocytes) provides a presumptive diagnosis, allowing immediate treatment. For penile discharge, microscopy of Gram-stained urethral smears has a sensitivity of 90–95% [23]. Microscopy of Gram-stained endocervical smears is less sensitive (30–50%) [23]. Microscopy is not used for pharyngeal specimens, as commensal species of *Neisseria* reside in the throat, which cannot be distinguished from *N. gonorrhoea* on Gram stain. NAAT is the preferred method for gonorrhoea screening using first pass urine, vaginal, cervical, rectal or throat specimens (Figure 1.4).

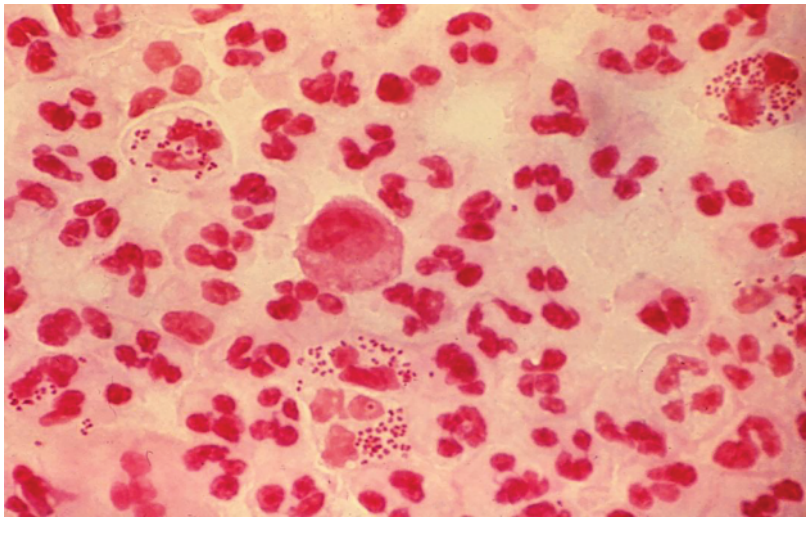

Figure 1.4 Urethral swab Gram's stain in patient with gonorrhoea [19]. Source: Joe Miller, 1979, Center for Disease Control (CDC) – PHIL/Public domain.

NAATs allow multiplex testing for chlamydial and gonococcal infections on a single specimen, and transport requirements for specimens are less stringent than for culture. To inform appropriate treatment, isolation of the organism by culture and antibiotic sensitivity testing is monitored as antimicrobial-resistant gonorrhoea is an important and emerging issue. The oropharyngeal gonococcal infections play an important role in the development of AMR in *N. gonorrhoeae* in the presence of commensal *Neisseria* species that can harbour genetic antibiotic resistance elements developed through prior antibiotic exposure [24]. Data from antimicrobial resistance testing is collected by laboratories to inform public health surveillance of this infection.

Treatment

Therapy with intramuscular *ceftriaxone 500 mg* is recommended for persons with uncomplicated gonococcal infections of the cervix, urethra, rectum or pharynx [14]. Some guidelines add 1000–2000 mg of *Azithromycin* in addition to the intramuscular *ceftriaxone* [25]. Persons who are diagnosed with gonorrhoea should be informed about the importance of contact tracing or partner notification, test of cure, when they can resume sexual activity, and STI risk reduction in future.

Viral STIs

HPV Infections

HPV infection is one of the most common STIs with approximately 40 subtypes that can potentially cause anogenital infection. The HPV types are classified based on their oncogenic potential as either low-risk (non-oncogenic) types or high-risk types (oncogenic types) (Table 1.1). Low-risk HPV types 6 and 11 cause approximately 90% of genital warts;

Table 1.1 Classification of HPV types.

Human Papillomavirus Types
Low-Risk Types (Non-Oncogenic)
• Associated with genital warts and benign or low-grade cellular changes (mild Pap test abnormalities).
• Approximately 90% of genital warts are caused by HPV types 6 and 11.
• The HPV types causing genital warts can occasionally cause lesions on oral, upper respiratory, upper gastrointestinal and ocular locations. Recurrent respiratory papillomatosis, a rare condition, is usually associated with HPV types 6 and 11.
High-Risk Types (Oncogenic)
• Associated with low-grade cervical cellular changes, high-grade cervical cellular changes (mild, moderate and severe Pap test abnormalities), and cervical dysplasia. In rare cases, associated with anogenital (i.e. cervical, vulvar, vaginal, anal and penile) and oropharyngeal cancers.
• HPV types 16 and 18 account for approximately 63% of all HPV-associated cancers and about 66% of cervical cancers.
• The HPV types 31, 33, 45, 52 and 58 cause approximately 10% of all HPV-associated cancers.

Source: Reproduced with permission from Stankiewicz Karita and Spach [26].

high-risk HPV types 16 and 18 account for approximately 63% of all HPV-associated cancers and about 70% of cervical cancers; high-risk HPV types 31, 33, 45, 52 and 58 account for an additional 10% of cervical cancers [26–28].

Epidemiology

It is estimated that most sexually active men and women will acquire genital HPV infection at some point in their lives, but most infections are asymptomatic and resolve spontaneously. Genital warts represent a sexually transmitted benign condition caused by HPV infection, especially HPV6 and HPV11. Cervical cancer is the fourth most common female malignancy [29].

Virology, Pathogenesis and Transmission

HPV is a non-enveloped, double-stranded DNA virus, approximately 50–60 nm in diameter [26]. The viral DNA genome is comprised of six early (E1, E2, E4, E5, E6 and E7) proteins that maintain regulatory function (and can cause cell oncotransformation) and two late (L1 and L2) proteins that are involved in viral assembly [30, 31]. HPV has a characteristic icosahedral viral outer shell, primarily comprised of 72 star-shaped pentameric capsomeres [30, 32]. Each pentameric capsomer contains 5 HPV L1 proteins, and each virion contains 360 of the L1 proteins [28] (Figure 1.5). All these 72 pentameric capsomers have the unique ability to self-assemble and form the outer HPV shell; this self-assembling property is the key element used in the design and production of the self-assembling HPV vaccine [33]. The viral shell also contains up to 72 molecules of the L2 minor protein, which are believed to play a role linking the capsid to the HPV DNA [28, 34].

Infection with HPV occurs at the basal cell layer of stratified squamous epithelial cells. Infection stimulates cellular proliferation in the epithelium, and the infected cells display a broad spectrum of changes that include asymptomatic infection, benign hyperplasia (papilloma), oncogenic progression and invasive carcinoma [26, 35]. To effectively replicate, HPV must utilise the host cellular machinery. During the process, the viral protein product encoded by E6 binds to the p53 tumour suppressor gene product, which results in the premature degradation of the p53 protein [36]. The E7 protein binds to a tumour suppressor protein – the retinoblastoma protein – and inhibits its function [37]. The E6 and E7 proteins mediate much of the HPV oncogenic potential by assisting the cell in evading host immunity, a process that facilitates virion production in differentiating epithelial cells [26, 28, 35].

HPV infects the mucosa of the anogenital tract, oropharyngeal region, upper respiratory tract and the surface of the skin [15]. Transmission is through skin-to-skin contact with apparent or subclinical epithelial lesions and/or through genital fluids containing infective virus during sexual activity. Resultant microabrasions enable viral inoculation and infection of the basal cells of the epithelium. Viral replication occurs in the well-differentiated layers near the surface with virions being released from desquamating cells [15].

Clinical Features

Most HPV infections are transient, asymptomatic or subclinical, and, among immunocompetent individuals, have no clinical consequences. About 90% of HPV infections are cleared by the host immune system within two years of infection. Persons with clinically evident disease have a range of possible presentations that correlate with the HPV type and host

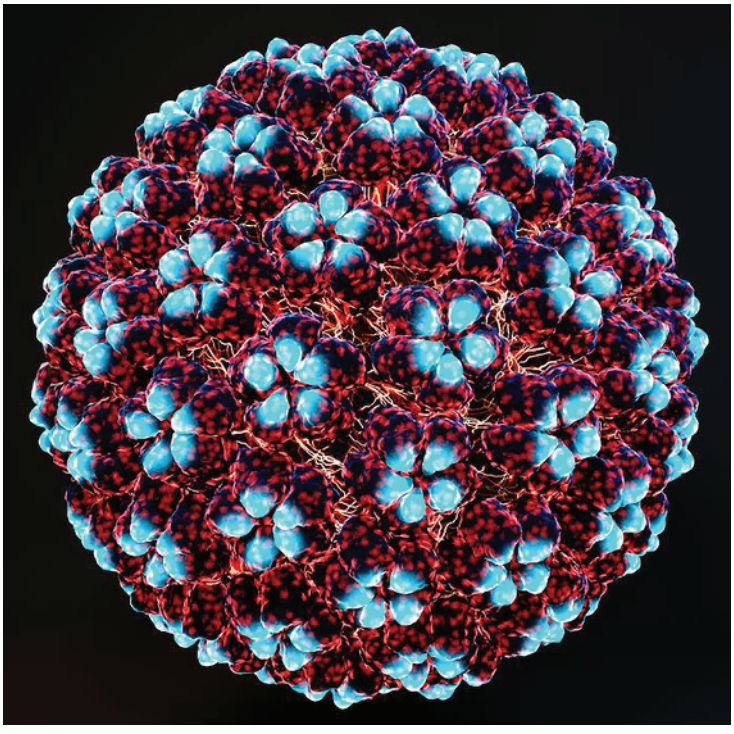

Figure 1.5 Human papillomavirus. Human papillomavirus is a small, non-enveloped, double-stranded DNA virus that is approximately 55 nm in diameter. The virus has an icosahedral shell primarily consisting of 360 molecules of the L1 major capsid protein arranged as a 72-pentameric capsomere (light blue). Source: Reproduced with permission from Stankiewicz Karita and Spach [26].

factors [26]. The most common clinically significant manifestations associated with HPV infection are anogenital warts, oral papillomas, oropharyngeal cancer, cervical cancer, cervical dysplasia, anal cancer and anal dysplasia [38, 39]. Although most precancerous lesions are not visible clinically, some will subsequently progress to form visible lesions or masses in the cervix or perianal region [26, 28].

Diseases of the oral cavity due to HPV infection include squamous papilloma, oral verrucae vulgaris, condyloma acuminatum and focal epithelial hyperplasia (Heck's disease) [6]. Squamous papilloma, associated with HPV types 6 and 11, primarily acquired through sexual activities, are the most common benign neoplasia of the oral epithelium, occurring predominantly on the soft palate, uvula and tongue. They may appear white due to keratinisation, are usually less than 1 cm in diameter, and may be fixed to the underlying tissue with a broad base (sessile) or have a stalk-like base (pedunculated) [6, 9, 40].

Verruca vulgaris, caused by HPV types 2, 4, 6 and 40 [41] are common cutaneous lesions with oral lesions affecting the keratinised tissues of the lip, hard palate and gingiva. They are solitary cauliflower-like lesions, the same colour as adjacent oral mucosa or white due to keratinisation. Transmission is often via autoinoculation of the oral or peri-oral structures from a cutaneous lesion on the finger [9].

Condyloma acuminata, caused by HPV types 6 and 11, otherwise known as genital warts, affect the anogenital epithelium but can be transmitted to the oral cavity by oral-genital contact. Oral lesions are larger than squamous papilloma and firmly adherent to underlying mucosa of the soft palate, lingual frenum and the tongue. Individual lesions coalesce to form larger lesions whose surface layer can have a cauliflower-like appearance or finger-like projections [6, 9].

Focal epithelial hyperplasia (Heck's disease) presents as small, single or multiple papules on the oral mucosa caused by infection with HPV types 13 and 32. They predominantly affect the labial and buccal mucosa, lower lip and tongue, and less commonly, the upper lip, gingiva and palate. Most lesions resolve on their own [42]. More information on HPV associated oral lesions is provided in Chapter 15.

Diagnosis

HPV types 16 and 18 are associated with approximately 70% of cervical cancers [43]. Cervical cancer screening programs rely on detecting 'high-risk' HPV types from samples of the cervix using nucleic acid hybridisation and/or cytology to identify abnormal cells and are important public health strategies employed worldwide. The oncogenic forms of HPV, types 16 and 18, are also associated with anal cancer and malignancies of the head, neck, oropharynx and oral cavity [44].

Diagnosis of HPV associated ano-genital and oral lesions relies on clinical assessment, removal and histological confirmation. Detection of a lesion during dental assessment should prompt referral with elective dental procedures being deferred until the lesion is diagnosed. The affected area should be recorded and re-examined for recurrence at each dental visit. Advising patients to stop smoking, reduce alcohol consumption and have regular dental checks is an important part of routine oral health care.

Treatment

Treatment for genital warts depends on the location of the wart. Treatments can be patient-administered (i) podophyllotoxin (Podofilox/Condylox), a derivative of podophyllin (a resin extract) with antimitotic properties and (ii) imiquimod (Aldara), a cytokine inducer that activates the cell-mediated immune system. Provider-administered treatments include (i) cryotherapy with liquid nitrogen, (ii) the caustic agents trichloroacetic acid (TCA) or bichloroacetic acid (BCA), and surgical removal [14]. Initial HPV treatments have clearance rates >50%, but recurrence is common. Treatment for cervical cancer involves chemotherapy with adjunctive radiation therapy. This type of treatment must be performed by a physician in a monitored setting due to adverse events associated with the administration of cytotoxic agents. Each cycle of chemotherapy/radiation can last multiple weeks, and patients may require several cycles to induce remission [26].

Prevention

Consistent use of latex male condoms can reduce the risk of sexual HPV transmission [14]. Vaccines can prevent diseases and cancers caused by HPV. The bivalent, quadrivalent and 9-valent HPV vaccines protect against most cervical cancer cases and the quadrivalent and 9-valent vaccines also protect against most genital warts [26]. Regular cervical cancer screenings with either pap smears or HPV DNA testing are one of the greatest preventive

measures for women to lower the risk of cancer-related death. Most importantly, it is important to note that HPV vaccination does not eliminate the need for women to have regular cervical cancer screenings [26].

HSV Infections

Genital herpes is caused by both HSV type 1 (HSV1) and HSV type 2 (HSV2), but HSV2 is the most common cause of genital ulcer disease worldwide. HSV1 commonly causes orolabial diseases (cold sores).

Epidemiology

HSV2 infection is widespread throughout the world with an estimated 491 million (13%) people aged 15–49 years worldwide living with the infection in 2016 [1].

Virology, Pathogenesis and Transmission

Both HSV1 and HSV2 are 150–200 nm α-herpesviruses that are structurally comprised of four major components: DNA, nucleocapsid, tegument and lipid envelope (Figure 1.6) [46, 47]. HSV genome is a single molecule of double-stranded DNA (approximately 152 000 base pairs that encode at least 74 genes); the DNA genome is surrounded by an icosahedral capsid, also referred to as the nucleocapsid or viral core [45]. The tegument, referred to as the matrix, is an amorphous protein-rich layer that surrounds the capsid. The envelope makes up the outermost part of HSV and consists of a lipid bilayer membrane studded with an array of 12 distinct types of glycoproteins. The glycoproteins are required for viral entry and elicit neutralising antibodies. Differences in glycoprotein G (gG) between HSV1 and HSV2 have been utilised in the development of HSV type-specific serologic tests [45].

During initial infection, HSV penetrates susceptible mucosal surfaces or abraded cracks into the skin. The virus is transported from epithelial cells to nerve endings and then along

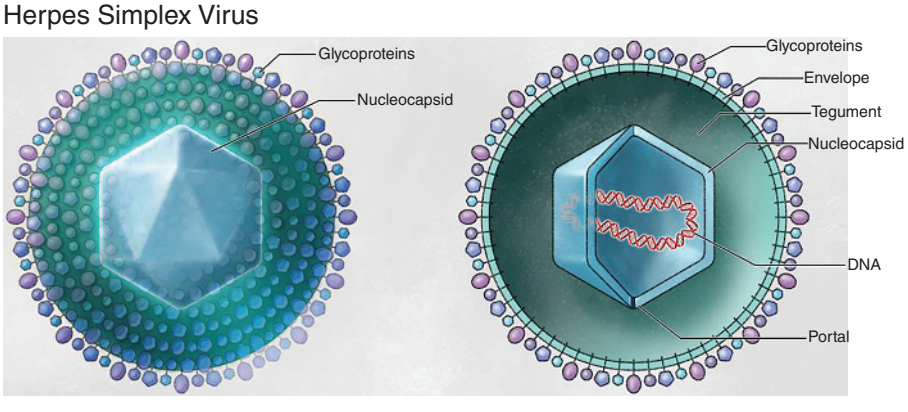

Figure 1.6 Basic structure of herpes simplex virus. Herpes simplex virus is approximately 150–200 nm in diameter. The basic structural features for HSV1 and HSV2 are the same. The image on the left depicts intact virion and that on the right shows cross-sectional view. Reproduced with permission. Source: Spach and Johnstone [45] – Illustration by Jared Travnicek, Cognition Studio.

peripheral nerve axons through retrograde transport. Once this transport is completed, HSV establishes persistent infection as an episome in the nerve cell bodies in the sacral ganglia and paraspinal ganglia [48]. In the ganglia, HSV enters a 'latent' state with an expression of viral microRNAs and the latency-associated transcript factors that are important for prevention of neuronal apoptosis, maintenance of latency and regulation of spontaneous viral reactivation [49–52]. Because HSV is not cleared from neurons, the ganglia become lifelong reservoirs for the virus [45].

Clinical Features

Traditionally, HSV2 was associated with genital disease with transmission to the genital skin through sexual contact whilst HSV1 predominantly caused oral ulceration. However, this distinction of HSV1 and HSV2 into respective sites of infection is outdated. Over the last 20 years, there has been a disproportionate rise in HSV1 as the cause of initial genital herpes infection through sexual contact in adolescence and adulthood, possibly resulting from fewer oral exposures in childhood. Conversely, HSV2 can also cause oral ulceration, although this is very uncommon compared with HSV1.

Clinical episodes of genital herpes are categorised as first-episode primary, nonprimary infection or recurrent symptomatic infection. Asymptomatic infection is common, and persons with asymptomatic or unrecognised genital herpes account for a substantial proportion of genital HSV infections [45].

Primary Genital Infection

Primary infection is defined as the first infection with either HSV1 or HSV2 in the absence of antibodies to HSV type. Primary genital infection is often symptomatic, but patients may have unrecognised or subclinical infection. With symptomatic infection, clinical manifestations of primary infection are typically more severe than recurrences and may include systemic systems and resolve within three weeks in the absence of antiviral therapy. Serum antibodies appear within 12 weeks of the primary infection in most people [45, 53, 54].

Nonprimary Infection

The term 'nonprimary HSV infection' most often refers to infection with HSV1 or HSV2 in an individual with pre-existing antibodies to the other virus. For example, a person may acquire oral HSV1 infection as a child and later acquire genital HSV2 as an adult. Manifestations of nonprimary infection tend to be milder than those of primary infection, presumably due to cross-immunity protection from prior infection with the other HSV type [45, 54, 55].

Recurrent Disease

Recurrent symptomatic genital herpes is characterised by mild, localised symptoms that typically are resolved within three to five days after onset. Prodromal symptoms (localised tingling and burning) due to HSV travelling along the nerve axons are common and begin 12–24 hours before lesions appear. Lesions typically form vesicles or pustules that progress to a wet ulcer and gradually become dry and crusted [45, 54].

Primary exposure of the oral mucosa to HSV1 (and occasionally HSV2) results in acute herpetic gingivostomatitis, typically 5–10 days after exposure to HSV. Features include

fever, sore throat and painful vesicles, often in a posterior location. The characteristic vesicle of HSV breaks down to form an ulcer, scabs and eventually heals. Both keratinised and non-keratinised oral surfaces may be involved with lesions commonly located on the buccal and gingival mucosa. In severe cases, dysphagia and lymphadenopathy may be present. In immunocompetent patients, the symptoms resolve spontaneously within 10–14 days [6]. The virus migrates to the sensory ganglion in the dorsal root, innervating the primary lesion, and remains latent after initial infection [56]. Reactivation of the virus in the oral environment occurs predominantly with HSV1, causing recurrent oral disease or asymptomatic shedding. HSV2 recurrences in the oral mucosa are less common but cause more genital recurrences overall [57]. The process by which reactivation occurs is not fully understood. Potential precipitating factors include local nerve stimulation, for example by trauma or UV light, and immunosuppression secondary to other conditions such as infection or malignancy. Persistent psychological stress has also been implicated [15]. Recurrent disease presents as grouped lesions progressing from erythematous papules and vesicles to ulcerating erosions, most commonly affecting the labial tissue and vermilion [6]. Oral HSV infections are described in Chapter 14. Recurrent intraoral HSV stomatitis infection is uncommon but typically results from HSV1 infection and produces vesicles and subsequent erosions on keratinised surfaces such as the alveolar ridge, the attached gingivae, hard palate and dorsal tongue [58].

Diagnosis

The clinical diagnosis of genital HSV is challenging because many persons with genital herpes do not develop the characteristic vesicular or ulcerative lesions. Further, less typical lesions, such as fissures, can mimic other conditions. Since the natural history and subsequent clinical course depend on whether HSV1 or HSV2 is the causative agent, the clinical diagnosis of genital herpes should be confirmed by laboratory testing, including HSV typing [45, 59].

Diagnosis of genital HSV1 and HSV2 relies upon polymerase chain reaction (PCR) of viral DNA isolated from a herpetic lesion. Concentrations of HSV are much greater in the vesicle and ulcer stages, so samples from these are preferred. Serology detects previous exposure to the herpes virus and is not useful for diagnosis as up to 80% of the general population will be sero-reactive for HSV1 and about 12% for HSV2, even in the absence of clinical symptoms, due to previous exposure to the virus.

Cytologic Examination

Cells infected with HSV will show characteristic changes, and these can be observed by obtaining a sample from the lesion and smearing it on a microscope slide (e.g. Tzanck smear). This test is not recommended due to low sensitivity (less than 80%) and lack of differentiation of HSV1 from HSV2 [45].

Treatment

Oral antiviral therapy offers clinical benefits to most patients with symptomatic herpes and is the mainstay of treatment. Antiviral therapy partially controls symptoms of genital herpes when used to treat first clinical and recurrent episodes (‘episodic therapy’), or when used daily to prevent recurrences or transmission (‘suppressive therapy’). Antiviral therapy

does not eradicate HSV, nor does it impact the risk, frequency or severity of recurrences after the medication is discontinued. Topical antiviral treatment is discouraged from clinical use since it offers less benefit than oral therapies [14]. Antiviral therapy with acyclovir, valacyclovir or famciclovir can be used intermittently for each episode of genital herpes (episodic therapy) and daily to prevent recurrent outbreaks (suppressive therapy) [45].

Dental treatment should be deferred during periods of active outbreaks of oral lesions, as retracting and stretching the skin can cause rupture of the vesicles and inoculation of the virus to adjacent skin. Aerosols or droplets created by high-speed hand pieces during procedures may contain viral particles that can infect dental staff or other areas of the patient such as the conjunctiva of the eye. Viral particles may be transmitted through tears in latex gloves, causing herpetic whitlow in the clinician. This lesion will resolve; however, dental clinicians should refrain from practice until the lesions have completely healed [9].

Prevention

Multiple strategies, including suppressive antiviral therapy, consistent use of condoms and disclosure of HSV status to partners, have been shown to reduce HSV transmission. Maximal efficacy in preventing HSV transmission is most likely achieved when a combination of these methods is used [45].

HIV Infection

HIV is a bloodborne viral pathogen that may be transmitted during unprotected sexual activity, sharing needles during injecting drug use, receiving HIV-infected organ and tissue transplants, or exposure of mucous membranes or non-intact skin with HIV-infected blood or other body fluids. HIV is a complex RNA virus of the genus *Lentivirus* within the Retroviridae family. HIV has an approximately 100 nm icosahedral structure with two single-stranded RNA molecules and 72 external spikes that are formed by the two major envelope glycoproteins, gp120 and gp41. Two major types of the HIV virus, HIV-1 and HIV-2, have been identified with HIV-1 being the most common worldwide and HIV-2 mostly found in western central Africa.

There were 37.7 million people living with HIV in 2020, up from 30.7 million in 2010, the result of continuing new infections and people living longer with HIV. Of the people living with HIV in 2020, 36 million were adults and 1.7 million were children under the age of 15 [60].

In untreated people with HIV, the disease typically progresses through three stages [61]:

Stage 1: Acute HIV infection. In this stage, infected people have a large amount of HIV in their blood. During this stage, they are highly infectious. Some people have flu-like illness with possible symptoms that may include fever, chills, rash, night sweats, muscle aches, sore throat, fatigue, swollen lymph nodes and mouth ulcers. This is the body's natural response to infection. Antigen/antibody or nucleic acid tests (NAT) are required to diagnose acute HIV infection.

Stage 2: Chronic HIV infection. This stage is also called asymptomatic HIV infection or clinical latency. HIV is still active but reproduces at lower levels. People may not have

any symptoms or get sick during this phase. This period may last 5–10 years or longer. People can transmit HIV in this phase. At the end of this phase, the viral load goes up and the CD4 cell count goes down. The person may have symptoms as the virus levels increase in the body, and the person moves into Stage 3.

Stage 3: Acquired immunodeficiency syndrome (AIDS). This is the most severe phase of HIV infection. People receive an AIDS diagnosis when their CD4 cell count drops below 200 cells mm^{-1}. At this stage, opportunistic infections may manifest and can have a high degree of morbidity and even mortality.

Oral Manifestations of HIV Infection

The most common oral manifestations of HIV/AIDS include oral candidiasis, linear gingival erythema, oral hairy leukoplakia, necrotizing ulcerative gingivitis and Kaposi sarcoma. HIV/AIDS and oral lesions in HIV disease are discussed in greater detail in Chapters 5 and 11, respectively.

Sexually Acquired Viral Hepatitis

Viral hepatitis is considered an STI as hepatitis A, B and C can potentially be transmitted through sexual contact. Hepatitis B and C are potentially life-threatening liver infections and a major global health problem.

Transmission of hepatitis A virus can occur from sexual activity with an infected person mainly through faecal–oral contact. People who are sexually active are considered at risk for hepatitis A if they are MSM (men who have sex with men), live with or have sex with an infected person. Vaccination is the most effective means of preventing hepatitis A transmission among people at risk for infection [62].

Hepatitis B can be transmitted through sexual activity. Unvaccinated adults who have multiple sex partners, along with sex partners of people with chronic hepatitis B infection, are at increased risk for transmission. Most infections are acquired in childhood, but adults can acquire it through injecting–drug use with sharing of needles and syringes, and sexual contact. Hepatitis B infection acquired in adulthood leads to chronic infection in less than 5% of cases, whereas infection in infancy and early childhood leads to chronic infection in about 95% of cases. Infection with the hepatitis B virus causes hepatocellular inflammation and necrosis. Chronic infection can lead to liver fibrosis, cirrhosis and hepatocellular carcinoma (HCC). Chronic hepatitis B infection can be treated but not cured with oral antiviral agents. WHO recommends the use of oral treatments (tenofovir or entecavir) as the most potent drugs to suppress the hepatitis B virus. Most people who start hepatitis B treatment must continue it for life. Hepatitis B can be prevented by vaccines that are safe, available and effective [62, 63].

Hepatitis C virus (HCV) infection is a common cause of chronic liver disease, leading in many cases to cirrhosis, decompensated disease, liver cancer and death. It is the major cause of liver cancer and liver transplants. Although not common, hepatitis C can be transmitted through sexual activity, mainly in MSM with specific sexual and other risk factors [64]. Having an STI, having sex with multiple partners, engaging in high-risk anal sexual practices (i.e. fisting) and use of recreational drugs appear to increase the risk of acquiring hepatitis C in MSM [64]. MSM with multiple sex partners who are coinfected

with HCV and HIV has been shown to be at increased risk of transmission of hepatitis C. There is no vaccine for hepatitis C. Hepatitis C has become a curable disease with the use of antiviral agents (>95%) [62].

Molluscum Contagiosum Virus Infection

Molluscum contagiosum virus (MCV) is a large DNA virus belonging to the family of poxviridae, and has four subtypes MCV1–4 [15]. MCV replicates in the cytoplasm of infected epithelial cells, presenting clinically as molluscum contagiosum with MVC1–4 being indistinguishable. Transmission occurs by direct skin-to-skin contact, which is facilitated by microabrasions and a warm, moist environment. Infectivity and extensive lesions may indicate advanced HIV infection. Diagnosis is usually made by clinical assessment, histology may show the presence of large intracytoplasmic inclusion bodies (Henderson–Patterson bodies) [65], and viral shedding occurs whilst lesions are present. Transmission can be occurred by physical contact and through fomite transmission from sharing towels. Sexual contact results in genital infection presenting as smooth, pearly, umbilicated lesions in the pubic area, thighs, buttocks and less commonly the external genitalia where it spares the mucous membranes. Autoinoculation can result in infection of the cutaneous lip and perioral skin. Lesions at these sites are flesh coloured, dome shaped, smooth or umbilicated 3–5 mm papules, often occurring in clusters [6]. They are more prevalent in the immunocompromised state.

Other STIs and Conditions

Trichomonas vaginalis (TV), a flagellated protozoan of the order Trichomonadida, is parasitic to the genitourinary tract and is the most common curable STI in the world. It does not have any oral manifestations. TV presents as a profuse malodourous vaginal discharge and vulvovaginitis in women. In 2–5% of infected women, a 'strawberry cervix' is seen on examination caused by small punctate cervical haemorrhages from the whipping motion of four anterior flagella. TV is an important diagnosis to make in pregnancy as it may be associated with premature rupture of membranes, pre-term delivery and low birth weight. TV is asymptomatic in up to 75% of men, with the most common symptom being urethral discharge. TV may be a cofactor in HIV transmission. Testing is performed using NAATs on first pass urine or high vaginal swab and/or microscopy with identification of motile protozoa propelled by flagella at 400× magnification.

Mycoplasma genitalium is a slow growing and difficult to isolate bacterium [14], preferentially colonising the urethra where it can invade epithelial cells. It is mainly transmitted by genito-genital mucosal contact with limited oral–genital transmission as oral carriage is low. It is an emerging bacterial STI, causing urethral discharge and dysuria in men and cervicitis and occasionally intermenstrual bleeding, post-coital bleeding and pelvic pain in women. Diagnosis is by NAAT on first pass urine and/or high vaginal swabs with macrolide resistance probe testing if positive to identify resistance mutations [14]. Antimicrobial resistance is a major concern in the treatment of *M. genitalium* [66] and testing and treatment may be done in consultation with a specialist.

Bacterial vaginosis (BV) is characterised by disruption of the vaginal flora with the overgrowth of anaerobic bacteria such as *Gardnerella vaginalis, Prevotella species, Mobiluncus species, Ureaplasma urealyticum and Mycoplasma hominis* replacing normally dominant *Lactobacillus* spp, thereby producing an altered vaginal discharge in women [14, 67]. BV has been implicated in PID, poor obstetric outcomes including miscarriage, preterm birth and low birth weight and increased risk of HIV acquisition [67]. Diagnosis relies on clinical features, raised vaginal pH and classical microscopic findings on Gram-stained or wet preparations of vaginal discharge.

Vulvovaginal candidiasis (VVC) is a common cause of vaginal discharge in women, and balanitis in men, most commonly due to the fungus *Candida albicans*, diagnosed by classical features of hyphae, pseudo-hyphae and spores on microscopy of a wet preparation of vaginal discharge [14]. Topical formulations of antifungal such as clotrimazole effectively treat uncomplicated VVC.

Chancroid, a rare bacterial STI, caused by the bacterium *Haemophilus ducreyi*, is characterised by painful ulceration and tender inguinal lymphadenopathy (bubo). Diagnosis relies on PCR testing of material obtained from the base of the ulcer or culture of the ulcer material [14] or pus aspirated from the bubo.

Donovanosis, another rare bacterial STI, caused by the Gram-negative bacterium *Klebsiella granulomatis*, causes chronic, slowly progressive ulceration of the genitalia. Diagnosis relies upon direct microscopy of tissue crush smear or biopsy from a lesion stained with Giemsa stain, identifying characteristic 'Donovan bodies' [14].

Scabies and pediculosis pubis (pubic lice) are genital infestations with *Sarcoptes scabiei* and *Phthirus pubis*, respectively. These are transmitted by intimate skin-to-skin contact often during sexual activity. Pubic lice are diagnosed by direct visualisation (with or without low power microscopy). Scabies is a clinical diagnosis based on the clinical finding of symmetrical polymorphic lesions on the hands (especially the finger webs), wrists, axillae, buttocks and genitals. Microscopic examination of skin scrapings allows visualisation of the mite [14].

References

1 World Health Organization (2021). Sexually transmitted infections (STIs) Fact sheet. https://www.who.int/news-room/fact-sheets/detail/sexually-transmitted-infections-(stis).

2 Spach, D.H. and Mirchandani, M.S. (2021). Syphilis. 2e. National STD program, University of Washington, USA. Available from: https://www.std.uw.edu/go/comprehensive-study/syphilis/core-concept/all.

3 World Health Organization (2021). Web Annex 2. Data methods. Global progress report on HIV, viral hepatitis and sexually transmitted infections, 2021 Accountability for the global health sector strategies 2016–2021: actions for impact [Internet]. Geneva: World Health Organization Licence: CC BY-NC-SA 3.0 IGO. http://apps.who.int/iris/bitstream/handle/10665/342813/9789240030992-eng.pdf.

4 Izard, J., Renken, C., Hsieh, C.E. et al. (2009). Cryo-electron tomography elucidates the molecular architecture of *Treponema pallidum*, the syphilis spirochete. *J. Bacteriol.* 191 (24): 7566–7580.

5 Hook, E.W. 3rd. (2017). Syphilis. *Lancet* 389 (10078): 1550–1557.
6 Bruce, A.J. and Rogers, R.S. 3rd. (2004). Oral manifestations of sexually transmitted diseases. *Clin. Dermatol.* 22 (6): 520–527.
7 Hook, E.W. III and Marra, C.M. (1992). Acquired syphilis in adults. *N. Engl. J. Med.* 326 (16): 1060–1069.
8 Ghanem, K.G., Ram, S., and Rice, P.A. (2020). The modern epidemic of syphilis. *N. Engl. J. Med.* 382 (9): 845–854.
9 NetCE (2021). Oral Manifestations of Sexually Transmitted Infections: NetCE. https://www.netce.com/coursecontent.php?courseid=1680.
10 Oswal, S. and Lyons, G. (2008). Syphilis in pregnancy. *Contin. Educ. Anaesth. Crit. Care Pain* 8 (6): 224–227.
11 Pregnancy Care Guidelines: Syphilis [22 May 2021]. Available from: www.health.gov.au/resources/pregnancy-care-guidelines/part-f-routine-maternal-health-tests/syphilis#.
12 Pessoa, L. and Galvão, V. (2011). Clinical aspects of congenital syphilis with Hutchinson's triad. *Case Rep. Dermatol.* 2011: bcr1120115130.
13 Hillson, S., Grigson, C., and Bond, S. (1998). Dental defects of congenital syphilis. *Am. J. Phys. Anthropol.* 107 (1): 25–40.
14 Workowski, K.A., Bachmann, L.H., Chan, P.A. et al. (2021). Sexually Transmitted Infections Treatment Guidelines, 2021. *MMWR Recomm. Rep.* 70 (4): 1–187.
15 Pattman, R., Sankar, N., Elawad, B. et al. (2010). *Oxford Handbook of Genitourinary Medicine, HIV, and Sexual Health*. Oxford: Oxford University Press.
16 Darville, T. and Hiltke, T.J. (2010). Pathogenesis of genital tract disease due to *Chlamydia trachomatis*. *J Infect Dis* 201 (Suppl 2): S114–S125.
17 David, H. and Spach, S.J. (2021).Chlamydial infections. https://www.std.uw.edu/go/comprehensive-study/chlamydial-infections/core-concept/all1
18 Öztürk, Ö. and Seven, H. (2012). *Chlamydia trachomatis* tonsillopharyngitis. *Case Rep. Otolaryngol.* 2012: 736107.
19 Spach, D. (2021). Gonococcal infection. https://www.std.uw.edu/go/comprehensive-study/gonococcal-infections/core-concept/all.
20 Cohen, M.S. and Cannon, J.G. (1999). Human experimentation with *Neisseria gonorrhoeae*: progress and goals. *J Infect Dis* 179 (Suppl 2): S375–S379.
21 Quillin, S.J. and Seifert, H.S. (2018). Neisseria gonorrhoeae host adaptation and pathogenesis. *Nat. Rev. Microbiol.* 16 (4): 226–240.
22 Hill, S.A., Masters, T.L., and Wachter, J. (2016). Gonorrhea – an evolving disease of the new millennium. *Microb. Cell.* 3 (9): 371–389.
23 Bignell, C. and FitzGerald, M. (2011). UK national guideline for the management of gonorrhoea in adults, 2011. *Int. J. STD AIDS* 22 (10): 541–547.
24 Adamson, P.C. and Klausner, J.D. (2021). The staying power of pharyngeal gonorrhea: implications for public health and antimicrobial resistance. *Clin. Infect. Dis.* 73 (4): 583–585.
25 Unemo, M., Ross, J., Serwin, A.B. et al. (2020). European guideline for the diagnosis and treatment of gonorrhoea in adults. *Int. J. STD AIDS* 2020: 956462420949126.
26 Helen C., Karita, S. and Spach, D.H. (2021). Human Papilloma virus. https://www.std.uw.edu/go/comprehensive-study/hpv/core-concept/all.
27 de Sanjose, S., Quint, W.G., Alemany, L. et al. (2010). Human papillomavirus genotype attribution in invasive cervical cancer: a retrospective cross-sectional worldwide study. *Lancet Oncol.* 11 (11): 1048–1056.

28 Schiffman, M., Doorbar, J., Wentzensen, N. et al. (2016). Carcinogenic human papillomavirus infection. *Nat. Rev. Dis. Primers.* 2: 16086.

29 Arbyn, M., Weiderpass, E., Bruni, L. et al. (2020). Estimates of incidence and mortality of cervical cancer in 2018: a worldwide analysis. *Lancet Glob. Health* 8 (2): e191–e203.

30 Doorbar, J. (2006). Molecular biology of human papillomavirus infection and cervical cancer. *Clin. Sci. (Lond.)* 110 (5): 525–541.

31 Sapp, M. and Day, P.M. (2009). Structure, attachment and entry of polyoma- and papillomaviruses. *Virology* 384 (2): 400–409.

32 Buck, C.B., Day, P.M., and Trus, B.L. (2013). The papillomavirus major capsid protein L1. *Virology* 445 (1–2): 169–174.

33 Schiller, J.T. and Davies, P. (2004). Delivering on the promise: HPV vaccines and cervical cancer. *Nat. Rev. Microbiol.* 2 (4): 343–347.

34 Wang, J.W. and Roden, R.B. (2013). L2, the minor capsid rotein of papillomavirus. *Virology* 445 (1–2): 175–186.

35 McBride, A.A. (2022). Human papillomaviruses: diversity, infection and host interactions. *Nat. Rev. Microbiol.* 20: 95–108.

36 Mantovani, F. and Banks, L. (2001). The human papillomavirus E6 protein and its contribution to malignant progression. *Oncogene* 20 (54): 7874–7887.

37 Pang, C.L. and Thierry, F. (2013). Human papillomavirus proteins as prospective therapeutic targets. *Microb. Pathog.* 58: 55–65.

38 Centers for Disease Control and Prevention (2021). Cancers Associated with Human Papillomavirus, United States—2014–2018. USCS Data Brief, no. 26. Atlanta, GA: Centers for Disease Control and Prevention, US Department of Health and Human Services.

39 Van Dyne, E.A., Henley, S.J., Saraiya, M. et al. (2018). Trends in human papillomavirus–associated cancers—United States, 1999–2015. *Morb. Mortal. Wkly. Rep.* 67 (33): 918.

40 Lynch, D.P. (2000). Oral viral infections. *Clin. Dermatol.* 18 (5): 619–628.

41 Lukes, S.M. and Meneses, M. (2010). The dental hygienist's role in HPV recognition. *Dimensions Dental Hyg.* 8 (6): 72–77.

42 Ozden, B., Gunduz, K., Gunhan, O., and Ozden, F.O. (2011). A case report of focal epithelial hyperplasia (Heck's disease) with PCR detection of human papillomavirus. *J. Maxillofacial Oral Surg.* 10 (4): 357–360.

43 Bosch, F.X., Burchell, A.N., Schiffman, M. et al. (2008). Epidemiology and natural history of human papillomavirus infections and type-specific implications in cervical neoplasia. *Vaccine* 26: K1–K16.

44 Patton, L.L. (2015). *The ADA Practical Guide to Patients with Medical Conditions*. Wiley.

45 Spach, D.H and Johnstone, C. (2021). Herpes simplex virus. https://www.std.uw.edu/go/comprehensive-study/genital-herpes/core-concept/all.

46 Kukhanova, M.K., Korovina, A.N., and Kochetkov, S.N. (2014). Human herpes simplex virus: life cycle and development of inhibitors. *Biochemistry (Mosc.)* 79 (13): 1635–1652.

47 Whitley, R.J. and Roizman, B. (2001). Herpes simplex virus infections. *Lancet* 357 (9267): 1513–1518.

48 Cunningham, A.L., Diefenbach, R.J., Miranda-Saksena, M. et al. (2006). The cycle of human herpes simplex virus infection: virus transport and immune control. *J Infect Dis* 194 (Suppl 1): S11–S18.

49 Schiffer, J.T. and Corey, L. (2013). Rapid host immune response and viral dynamics in herpes simplex virus-2 infection. *Nat. Med.* 19 (3): 280–290.

50 Perng, G.C., Jones, C., Ciacci-Zanella, J. et al. (2000). Virus-induced neuronal apoptosis blocked by the herpes simplex virus latency-associated transcript. *Science* 287 (5457): 1500–1503.

51 Umbach, J.L., Kramer, M.F., Jurak, I. et al. (2008). MicroRNAs expressed by herpes simplex virus 1 during latent infection regulate viral mRNAs. *Nature* 454 (7205): 780–783.

52 Perng, G.-C. and Jones, C. (2010). Towards an understanding of the herpes simplex virus type 1 latency-reactivation cycle. Interdiscip Perspect. *Infect. Dis.* 2010: 262415.

53 Ashley-Morrow, R., Krantz, E., and Wald, A. (2003). Time course of seroconversion by HerpeSelect ELISA after acquisition of genital herpes simplex virus type 1 (HSV-1) or HSV-2. *Sex. Transm. Dis.* 30 (4): 310–314.

54 Sawleshwarkar, S. and Dwyer, D.E. (2015). Antivirals for herpes simplex viruses. *Br. Med. J.* 351: h3350.

55 Langenberg, A.G., Corey, L., Ashley, R.L. et al. (1999). A prospective study of new infections with herpes simplex virus type 1 and type 2. Chiron HSV Vaccine Study Group. *N. Engl. J. Med.* 341 (19): 1432–1438.

56 Cook, M.L. and Stevens, J.G. (1973). Pathogenesis of herpetic neuritis and ganglionitis in mice: evidence for intra-axonal transport of infection. *Infect. Immun.* 7 (2): 272–288.

57 Scott, D., Coulter, W., and Lamey, P.J. (1997). Oral shedding of herpes simplex virus type 1: a review. *J. Oral Pathol. Med.* 26 (10): 441–447.

58 Bruce, A.J. and Rogers, R.S. (2003). Acute oral ulcers. *Dermatol. Clin.* 21 (1): 1–15.

59 Engelberg, R., Carrell, D., Krantz, E. et al. (2003). Natural history of genital herpes simplex virus type 1 infection. *Sex. Transm. Dis.* 30 (2): 174–177.

60 UNAIDS (2021). Global HIV & AIDS statistics –fact sheet, World AIDS Day https://www.unaids.org/en/resources/fact-sheet.

61 Centre for Disease Control and Prevention. About HIV/AIDS. HIV Basics. https://www.cdc.gov/hiv/basics/whatishiv.html.

62 Gilson, R. and Brook, M.G. (2006). Hepatitis A, B, and C. Sexually transmitted infections. 82 (Suppl 4): iv35–iv39.

63. World Health Organization (2021). Hepatitis B https://www.who.int/news-room/fact-sheets/detail/hepatitis-b.

64 Nijmeijer, B.M., Koopsen, J., Schinkel, J. et al. (2019). Sexually transmitted hepatitis C virus infections: current trends, and recent advances in understanding the spread in men who have sex with men. *J. Int. AIDS Soc.* 22 (Suppl 6): e25348.

65 Whitaker, S.B., Wiegand, S.E., and Budnick, S.D. (1991). Intraoral molluscum contagiosum. *Oral Surg. Oral Med. Oral Pathol.* 72 (3): 334–336.

66 Machalek, D.A., Yusha, T., Shilling, H. et al. (2020). Prevalence of mutations associated with resistance to macrolides and fluoroquinolones in *Mycoplasma genitalium* : a systematic review and meta-analysis. *Lancet Infect. Dis.* 20 (11): 1302–1314.

67 Marrazzo, J.M., Martin, D.H., Watts, D.H. et al. (2010). Bacterial vaginosis: identifying research gaps proceedings of a workshop sponsored by DHHS/NIH/NIAID. *Sex. Transm. Dis.* 37 (12): 732–744.