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Sexually Transmitted Infections in the Tropics

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1. Introduction

The burden of sexually transmitted infections (STIs) on the health and well-being of the population in the developing world is considerable. The World Health Organization (WHO) estimates that there are 340 million new cases of curable STIs in the world each year; 174 million new cases of trichomoniasis, 92 million new cases of *Chlamydia* infection, 62 million cases of gonorrhea, and 12 million new cases of syphilis (Table 1). Approximately three quarters of these infections are in countries encompassing tropical regions of the world in Latin America, sub-Saharan Africa, and South and Southeast Asia. The prevalence of viral STIs is even higher; infection with Herpes simplex virus-2 (HSV-2) is the most common STI worldwide and as many as 50% of sexually active individuals will be infected with human papillomavirus (HPV) during their life. The prevalence of STIs is considerably greater than many classical tropical diseases and it is unfortunate that they do not receive more attention and resources from international programs and donor groups. The public health impact of these diseases extends well beyond the immediate effects and morbidities of infection. STIs have been implicated in facilitating acquisition and transmission of HIV, in pregnancy complications such as pre-term births, low birth weight infants, stillbirth, neonatal death and blindness, in the inducement of cervical and prostate cancers, and in increased risk of pelvic inflammatory disease and infertility. Failure to diagnose and treat STIs at an early stage thus increases the already substantial burden these conditions impose on the populations of developing countries. Although effective diagnostic tests and treatments are available for these STIs, they are often unavailable or inaccessible in resource-limited tropical settings. As a consequence, syndromic management of STIs remains the option of choice for individual case management. The inadequate public health response coupled to ongoing socioeconomic and demographic trends have led to an epidemic of STIs in many countries in the developing world. The development of antimicrobial resistance is an on-going problem and new agents are often much more expensive, increasing the burden of control. The economic costs of these diseases and their infection sequelae place a considerable burden on national health budgets and household income. In developing countries, STIs are among the top five reasons for which adults seek medical care. Due to the prevalence and public health implications of STIs in the tropics a discussion of STIs should be included in any compilation of tropical medicine.

This chapter will cover sexually transmitted infections caused by *Trichomonas vaginalis* (trichomoniasis), *Chlamydia trachomatis* (chlamydia and lymphogranuloma venereum), *Neisseria gonorrhoeae* (gonorrhea), *Treponema pallidum* (syphilis), *Haemophilus ducreyi*

(chancroid), *Calymmatobacterium granulomatis* (granuloma inguinale or donovanosis), and the viral STIs, herpes simplex virus and human papilloma virus. Each of these STIs spreads via vaginal, anal, and oral sex, as well as by inoculation of material from infected sores in some cases. All share many common risk factors and higher rates of infection are seen in marginalized populations; persons of low socioeconomic status, commercial sex workers, alcohol abusers, illicit drug users, men who have sex with men, prison populations, uncircumcised men, and those with multiple sex partners or who have partners with multiple sex partners. This chapter will cover both syndromic management of STIs as practiced in most areas of the tropical world (WHO 2003, 2005, 2007b) as well as individual descriptions of these diseases, their clinical presentation, diagnosis, and treatment. The treatment regimens presented are those recommended by the Centers for Disease Control and Prevention (CDC, 2010) and the World Health Organization (WHO, 2005).

	Latin America & the Caribbean	Sub-Saharan Africa	North Africa & Middle East	Southeast & South Asia	World Total
Trichomoniasis	18.5	32	5	76.5	174
Chlamydia	9.5	16	3	43	92
Gonorrhea	7.5	17	1.5	27	62
Syphilis	3	4	0.37	4	12
Total STIs	38.5	69	10	151	340
HIV/AIDS	1.4	22.5	0.46	4.1	33.3

Table 1. World Health Organization estimates of new cases of curable sexually transmitted infections and HIV, in millions (WHO, 2001; UNAIDS, 2010).

2. STIs and HIV

It is estimated that there are 34 million cases of HIV in the world with 68% or 22.5 million cases occurring in sub-Saharan Africa, where the prevalence is highest, and 4.1 million in South and Southeast Asia. The emergence of the HIV epidemic has complicated the control of STIs as HIV induced immunosuppression leads many patients to respond poorly to STI treatment regimens, requiring higher drug dosages and longer treatment schedules to affect cure. Sexually transmitted infections (STIs) also facilitate the transmission of other STIs, including human immunodeficiency virus (HIV). Several observational studies have been conducted that conclude there to be a strong association between STI and increased risk of HIV acquisition. An individual with a co-existing STI has a 2-5 fold greater risk of acquiring and transmitting HIV. Increased risk of HIV transmission has mostly been attributed to ulcerative STIs, mainly HSV-1 and 2, but also syphilis, chancroid, lymphogranuloma venereum, and granuloma inguinale. For instance the population attributable risk percent of HIV acquisition for HSV-1 and 2 varies from 15-30% in Africa. However, studies also show that non-ulcerative STIs, gonorrhea, *Chlamydia*, and trichomoniasis increase the risk of HIV transmission and acquisition as well. Studies that have examined non-ulcerative STIs and risk of HIV seroconversion have found an odds ratio of 1.8-4.8 for gonorrhea, 1.8-3.6 for chlamydia, and 1.9 for trichomoniasis. Therefore, early diagnosis and treatment of treatable

STIs could significantly impact the incidence of HIV transmission and acquisition. The number of individuals co-infected with HIV and an STI are high. Studies show increases in treatment failure of treatable STIs in HIV-positive patients. Studies in several countries show high treatment failure of syphilis in HIV-positive patients and in a trichomoniasis study, 18% of HIV-positive women were *T. vaginalis* positive 1 month after treatment. It is therefore possible that more aggressive treatment of non-ulcerative STIs may be necessary to cure an infection in HIV-positive individuals. STI treatment has been shown to significantly reduce HIV-shedding in both men and women. Follow-up for test of cure is also necessary due to the higher risk of treatment failure due to co-infection.

3. Syndromic management

The diagnosis and management of STIs in the tropics has a dual nature. Sophisticated testing equipment and facilities comparable to those available in developed nations can often be found in large urban centers and popular resort destinations in developing countries. However, in many parts of the developing world, the absence of etiologic diagnostic capacity due to constraints imposed by cost, lack of equipment or trained personnel, and time management has forced health care providers to rely on a syndrome-based approach to STI management. This approach employs clinical algorithms based on an STI syndrome to determine antimicrobial therapy. The following sections discuss management of the most common clinical syndromes encountered in STIs. Sexual partners of the index patient should also be examined for STIs and promptly treated for the same condition as treatment failures are common when partners are not treated. Often, treatment regimens to cover multiple infectious agents are recommended due to the difficulty in distinguishing between the overlapping clinical presentations of different STIs, the high prevalence of mixed infections in many areas, and to ensure adequate therapy in the case of loss to follow-up. Syndromic management enables many STIs to be treated and resolved at local clinics which may lack all but the most rudimentary laboratory capabilities. However, patients that do not respond to therapy or those that show systemic signs indicative of other disease conditions warrant referral to a clinic with more comprehensive facilities.

3.1 Urethral discharge in men

Neisseria gonorrhoeae and *Chlamydia trachomatis* are the major STI pathogens causing urethral discharge. In the syndromic management scheme, treatment of men with urethral discharge should cover both of these organisms. Treatment regimens may be found in the specific sections describing these STIs. Single-dose therapies are preferred. Whenever possible microscopic examination of the urethral smear should be performed; the appearance of more than 5 polymorphonuclear leukocytes per high power field (x1000) is indicative of urethritis. A Gram stain could also demonstrate the presence of gonococci and permit specific treatment. Patients should return in 7 days if symptoms persist. Treatment failure may be due to drug resistance necessitating use of one of the alternative drugs for these STI agents. Patients indicating poor compliance with therapy or the possibility of re-infection can be re-treated with the same drug regimen. *Trichomonas vaginalis* can also be a cause of urethritis in men. In areas of high local *T. vaginalis* prevalence, treatment for this organism should also be given at this time. If symptoms still persist, the patient should be referred to a facility possessing the resources for a more extensive workup.

3.2 Genital ulcers

Five STIs typically produce genital ulcers; herpes, syphilis, chancroid, lymphogranuloma venereum (LGV), and granuloma inguinale or donovanosis (Table 2). Physical examination should focus on the characteristics of the lesion(s): single or multiple, painless or painful, indurated or soft, irregular or regular borders, and how they began, as a papule or a vesicle. The examination should also determine the time since exposure, the presence or absence of lymphadenopathy, and the presence of systemic symptoms which may indicate another etiology. Syphilis ulcers are painless, indurated, sharply demarcated with a red, smooth base. When present, inguinal adenopathy is firm, rubbery, nontender and usually bilateral. Herpes ulcers begin as multiple grouped vesicles on a red base which forms shallow ulcers that may coalesce. Herpes inguinal adenopathy is bilateral, firm, and tender when present. Chancroid ulcers are shallow and often multiple with irregular shape, sharply demarcated borders, and undermined edges. Chancroid inguinal adenopathy is typically unilateral, fixed, and tender, with overlying erythema and may supperate. Granuloma inguinale ulcers are shallow sharply demarcated lesions with a beefy red friable base and usually without inguinal adenopathy. LGV ulcers are usually a single lesion, transient, and frequently not noticed. Inguinal adenopathy in LGV is usually unilateral, firm, tender, fixed, and may supperate or form fistulas. When genital ulcers present as vesicles only, syndromic management recommends treatment for both herpes infection and for syphilis if the patient has a positive RPR syphilis test, or has not received recent syphilis treatment. Patients with ulcers and no vesicles should be treated for syphilis plus either chancroid, granuloma inguinale, or lymphogranuloma venereum dependent on clinical presentation and local prevalence of these agents. In areas where herpes prevalence exceeds 30%, patients with ulcers should also be treated for herpes. Patients whose ulcers do not respond to both initial treatment and follow-up therapy should be referred for more extensive diagnostic testing.

Disease	Lesions	Lymphadenopathy	Systemic symptoms
Herpes	Small, painful, pruritic vesicles lesions shallow, usually multiple, grouped, and may coalesce	Tender, firm, bilateral nonsupperative inguinal adenopathy	Yes, primary infection
Primary Syphilis	Painless, indurated, round red smooth base, usually single, sharply demarcated	Nontender, firm, rubbery, nonsupperative, bilateral	None in primary stage Yes in secondary/tertiary
Chancroid	Tender, erythematous papules ulcers painful, purulent, irregular shape, soft undermined edges, often multiple	Tender, regional, painful, erythematous, supperative nodes, usually unilateral	None
LGV	Small, painless vesicle/papule usually single, heals rapidly often not noticed	Painful, matted, firm, large nodes supperate with fistula tracts, usually unilateral	After genital lesions heal spread to regional lymph nodes
Donovanosis	Small, painless pustules, ulcers shallow, erythematous, sharply demarcated, may expand, deepen, become necrotic, can be dry or nodular	Inguinal adenopathy usually absent	Yes, but rarely Extragenital lesions via inoculation from genital sores may occur

Table 2. Characteristics of Genital Ulcers

3.3 Inguinal bubo

Inguinal buboes are frequently associated with LGV and chancroid. If genital ulcers accompany the buboes, patients should be managed using the genital ulcer syndromic management approach. Inguinal buboes not accompanied by genital ulcer presentation should be treated with a regimen effective against LGV and chancroid. The recommended syndromic treatment is ciprofloxacin, 500 mg orally twice daily for 3 days plus doxycycline, 100 mg orally twice daily for 14 days, or erythromycin, 500 mg orally four times daily for 14 days. Some cases may require longer treatment than 14 days if the buboes are not resolved. Fluctuant lymph nodes can be aspirated through healthy skin. Incision and drainage or excision of nodes may delay healing.

3.4 Scrotal swelling

There are multiple infectious causes for epididymitis as well as non-infectious causes such as trauma, testicular torsion, and tumor. Patients with testis that are rotated or elevated or with a history of trauma should be referred for surgical option. An STI is more likely the cause for men under 35 years of age than for older men. An epididymitis which is accompanied by urethral discharge should be treated with drugs for both gonococcal and chlamydial infection.

3.5 Vaginal discharge

An abnormal vaginal discharge in terms of quantity, color, or odor most commonly results from vaginal infection. *Trichomonas vaginalis* is the most common STI cause of vaginal infection, though bacterial vaginosis (BV) and yeast infections also produce vaginal discharge. All women presenting with vaginal discharge should be treated for trichomoniasis and BV, in the absence of specific diagnosis, with metronidazole, 400-500 mg orally twice daily for 7 days. Metronidazole is not recommended in the first trimester of pregnancy. Pregnant women should be treated with metronidazole, 200-250 mg orally 3 times daily for 7 days. In rare cases, vaginal discharge may result from a mucopurulent cervicitis due to infection with *N. gonorrhoeae* or *C. trachomatis*. Treatment for cervical infection in women presenting with vaginal discharge is dependent on the local prevalence of these STIs. Women in high risk areas for *N. gonorrhoeae* or *C. trachomatis* with vaginal discharge and evidence of cervicitis should be offered treatment for these STIs in addition to treatment for BV and trichomoniasis.

3.6 Lower abdominal pain

There are multiple causes of lower abdominal pain in sexually active women in addition to pelvic inflammatory disease (PID) caused by STIs. Women presenting with lower abdominal pain and a missed or overdue period, pregnant, recent delivery, abortion, or miscarriage, abdominal guarding and/or tenderness, abnormal vaginal bleeding, or abdominal mass, should be referred for surgical or gynecological assessment. In the absence of these signs women with lower abdominal pain accompanied by cervical excitation tenderness or lower abdominal tenderness and vaginal discharge should be managed for PID. The etiologic agents for PID include *N. gonorrhoeae*, *C. trachomatis*, *T. vaginalis*, anaerobic and facultative bacteria, and perhaps *Mycoplasma*. When diagnostic capacity to distinguish these agents is absent the treatment regimen must be effective against all these

pathogens. The recommended syndromic treatment is a single dose therapy for gonorrhea, plus doxycyline, 100 mg orally twice daily, or tetracycline, 500 mg orally 4 times daily for 14 days, plus metronidazole, 400-500 mg orally twice daily for 14 days. Patients who do not respond to therapy within three days should be referred for a more complete diagnostic evaluation.

3.7 Neonatal conjunctivitis

Infants with neonatal conjunctivitis (ophthalmia neonatorum) present with eyes that are red, swollen and accompanied by discharge ("sticky eyes"). *Chlamydia trachomatis* and *N. gonorrhoeae* are the most significant pathogens which cause ophthalmia neonatorum in developing countries although infections from *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Haemophilus* spp., and *Pseudomonas* spp. occur. The oropharynx, urogenital tract, and rectum of neonates may also be affected in *Chlamydia trachomatis* or *N. gonorrhoeae* infection. *Neisseria* conjunctivitis develops within a few days of birth whereas *C. trachomatis* conjunctivitis develops slower, 5-14 days after birth. Neonatal conjunctivitis caused by *N. gonorrhoeae* can lead to blindness when untreated. Coverage should be provided for both of these STIs in settings where definitive diagnosis is not possible, especially where there is evidence of a maternal STI. Treatment should include a single dose therapy for gonorrhea and multiple dose therapy for chlamydia. For gonorrhea a single intramuscular injection of ceftriaxone, 50 mg/kg to a maximum of 125 mg total, should be administered. If ceftriaxone is unavailable, single injections of kanamycin or spectinomycin at 25 mg/kg to a maximum dose of 75 mg total may be used. For chlamydia treatment, erythromycin syrup, 50 mg/kg per day orally, in 4 divided doses for 14 days or trimethoprim, 40 mg with sulfamethoxazole, 200 mg orally twice daily for 14 days are recommended. Gonococcal ophthalmia neonatorum is preventable if a 1% silver nitrate solution or 1% tetracycline ointment is applied at birth as a prophylactic measure.

4. Trichomoniasis

Trichomonas vaginalis infects the urogenital tract of men and women, causing trichomoniasis. *Trichomonas vaginalis* is a member of the Phylum Zoomastigina, Class Parabasalia, Order Trichomonadida, and Family Trichomonadidae. *Trichomonas vaginalis* has only one life stage, trophozoites, which display various shapes including pyriform, ameboid, ellipsoidal, ovoidal, and spherical. The organisms measure between 10 – 30 microns. The organism possesses four anterior flagella and a fifth flagellum located posteriorly along the undulating membrane. These flagella of the organism yield the characteristic quivering motion of *T. vaginalis*.

4.1 Epidemiology

Trichomoniasis is the most common, curable, non-viral sexually transmitted infection worldwide. An estimated 174 million new cases of trichomoniasis occur worldwide each year. The incidence of *Trichomonas vaginalis* infection varies in different countries throughout the world. Incidence in Asian countries varies from 0.7% in rural China to 15.1% in sex workers in Indonesia. In South America, studies report incidence ranging from 4-9%. In Brazil prevalence is thought to have a range of 20 up to 40%. Incidence in African countries ranges from 2-20%. The incidence of trichomoniasis is higher in sexually active women over 25 years of age than in younger women.

4.2 Clinical manifestations

The actual number of new or existing cases of trichomoniasis is not known with complete surety because trichomoniasis is not a reportable disease and because of the significant number of asymptomatic cases. Trichomoniasis is usually asymptomatic in men, although sometimes it can cause non-gonococcal, non-chlamydial urethritis, epididymitis, and prostatitis. Clinical trichomoniasis in women ranges from asymptomatic carriers to flagrant vaginitis. Women have symptomatic disease more often than men. One third of asymptomatic woman will become symptomatic within 6 months of the onset of infection. Symptoms can include a vaginal discharge, vulvovaginal irritation and itching, painful urination or intercourse, foul odor, and lower abdominal pain. The presence or absence and severity of these symptoms determine whether the infection is classified as acute, chronic, or asymptomatic.

4.3 Health sequelae

Trichomoniasis is associated with a higher risk for other infectious diseases and adverse pregnancy outcomes such as preterm birth, premature rupture of placental membranes, and low birth weight infants. One study has also found an association between *T. vaginalis infection* in pregnancy and mental retardation in children. *Trichomonas vaginalis* infection is associated with pelvic inflammatory disease, especially PID leading to sterility. Trichomoniasis is significantly associated with HSV infection. *Trichomonas vaginalis* infection also increases the risk of human immunodeficiency virus (HIV) acquisition and the Centers for Disease Control and Prevention (CDC) estimates that as much as 20% of HIV transmission in the African American population in the United States may be attributable to *T. vaginalis* infection. *Trichomonas vaginalis* infection also increases the risk of cervical neoplasia and prostate cancer. Exposure to *T. vaginalis* results in a 2-fold increase in the risk of diagnosis of extraprostatic prostate cancer and a 3-fold increase in the risk of cancer that led to cancer-specific death. Thus, although trichomoniasis itself is a curable disease, *T. vaginalis* infection may indirectly be a life threatening disease.

4.4 Diagnosis

Because of the high prevalence of trichomoniasis, any woman seeking medical care for vaginal discharge should be tested for *T. vaginalis* infection. Trichomoniasis is traditionally diagnosed microscopically (wet mount) by observing mobile protozoa in vaginal secretions, cervical samples, or from urethral or prostatic swabs. However, this method has a relatively low sensitivity and requires immediate evaluation of a wet preparation slide for optimal results. The low sensitivity of this diagnostic method leads to under-diagnosis. The current gold standard for diagnosis of trichomoniasis is culture in Diamonds media and is widely used. Rapid antigen based point-of-care tests and nucleic acid based diagnostic tools are also available. Both of these techniques have high sensitivity and specificity. Papanicolaou (Pap) smear allows for direct visualization in saline prep and can be performed within 10-20 minutes of sample collection but is not widely used. The Whiff test can be performed by mixing vaginal secretions with 10% potassium hydroxide (KOH) to yield a strong fishy odor. This test has a poor specificity due to the fact that bacterial vaginosis can yield a similar result. All of the above mentioned diagnostic methods are applicable for diagnosis in women. In men, culture testing of urethral swabs, urine, or semen and the nucleic acid amplification tests are more sensitive diagnostic tools.

4.5 Treatment

Metronidazole, 2 g orally in a single dose or 500 mg orally twice a day for 7 days, is the treatment of choice for trichomoniasis. An estimated 2.5-10% of *T. vaginalis* infections show some degree of resistance to treatment; a resistance rate of 17.4% has been reported in Papua New Guinea. Treatment failures are higher in HIV-positive individuals. Recalcitrant cases may be treated with tinidazole at 2 g orally in a single dose. Consumption of alcohol should be avoided during treatment and for 24 hrs after completion of metronidazole therapy or 72 hours after completion of tinidazole therapy.

5. Chlamydia

Chlamydia trachomatis is a small, obligate intracellular bacterium that typically infects non-ciliated epithelial cells of mucous membranes; urethral epithelial cells in males and columnar epithelial cells of the endocervix in women. However in the lymphogranuloma venereum serovars, macrophages appear to be the principal host cell. *Chlamydia* is organized into multiple serovars that cause a diverse variety of human disease. Serotypes A, B, Ba, and C are the agents of classic blinding trachoma. Serotypes D thru K can cause adult inclusion and neonatal conjunctivitis, pneumonia, urogenital infections and Reiter's syndrome. Serotypes L1, L2, and L3 infect tissues deeper to the epithelium and cause lymphogranuloma venereum (LGV).

5.1 Epidemiology

Chlamydia infection is the most common bacterial STI in the world and among STIs, only the prevalences of herpes and trichomoniasis are higher. *Chlamydia* infection is highest in sexually active young adults under 25 years of age. *Chlamydia trachomatis* causes 30-50% of nongonoccal urethritis in men and mucopurulent cervicitis in women. In men less than 35 years of age *Chlamydia* is the principal cause of epididymitis. Although there is no lasting immunity and re-infection is common, women do clear the infection faster with increasing age. Lymphogranuloma venereum (LGV) is an uncommon disease and relatively rare in developed countries. The disease is most common in sub-Saharan Africa and is also reported in areas of the Caribbean, Central America, and Southeast Asia and sporadically in developed nations.

5.2 Clinical manifestations

Symptoms of chlamydial infection typically appear 1-3 weeks post exposure. Asymptomatic infection is common among both men, approximately ~50%, and women, approximately 70-80%. When it occurs, symptomatic infection clears spontaneously about 50% of the time. However, both untreated and asymptomatic infections can persist for years; as many as 10% remain infected after 3 years. Symptomatic men might have a urethral discharge and dysuria with burning and itching around the urethral opening. Epididymitis and prostatitis are sometimes present causing pain and swelling of the testes, fever, and rarely sterility. *Chlamydial* infection of the rectum can cause pruritis, rectal pain, discharge, or bleeding. Chlamydia infected women may experience cervicitis, vaginal discharge and dysuria. Infection and inflammation in the cervix may spread to the fallopian tubes and uterus, leading to pelvic inflammatory disease (PID). *Chlamydia* is among the most frequent pathogens associated with PID and up to 40% of women with untreated chlamydia develop PID. Some women with PID report lower abdominal pain, lower back pain, nausea, fever,

abnormal bleeding, and dysparenia but many women show no signs of infection. Untreated PID can result in chronic pelvic pain, tubal infertility in 10-20% of women, and occasionally potentially fatal ectopic pregnancy. Repeated infections increase the risk of adverse sequelae in both men and women. In rare cases persons with genital chlamydial infection can develop Reiter's syndrome, a triad of reactive arthritis accompanied by conjunctivitis and urethritis. Chlamydial infection, even asymptomatic disease, increases the risk of adverse pregnancy outcomes: premature rupture of membranes, preterm delivery and low birth weight. *Chlamydia* can easily pass to neonates during childbirth causing neonatal conjunctivitis and afebrile pneumonia in approximately 60% of those with infected mothers. The high levels of *Chlamydia* infection worldwide mean that there is substantial neonatal morbidity from perinatally transmitted chlamydial infection.

The *Chlamydia* serotypes which cause LGV are more virulent and more invasive than other chlamydial serotypes. The initial stage is a painless genital papule which heals rapidly and may be unrecognized. The organism then disseminates to regional lymph nodes, usually the inguinal nodes, where they replicate within macrophages and elicit a systemic response. This produces a painful inguinal lymphadenopathy, usually unilateral, by 2-6 weeks after the primary lesion often accompanied by fever, headache, and arthralgias. Rectal infection with LGV is characterized by a severe febrile proctocolitis, mimicking inflammatory bowel disease, with painful defecation, tenesmus, and less commonly a bloody mucopurulent discharge. Untreated LGV results in chronic inflammation with late fibrotic complications such as fistulas of the penis, urethra, and rectum, strictures, and genital lymphoedema and elephantiasis.

5.3 Diagnosis

Empirical evidence of *Chlamydia* infection is based on clinical presentation. The presence of greater than 10 polymorphonuclear leukocytes (PMNs) per 1000X field in vaginal discharge or 5 PMNs/field in urethral discharge is indicative of the cervicitis or urethritis characteristic of *Chlamydia* infection. There are currently no widely available point-of-care tests for *Chlamydia* infections. Most *Chlamydia* infections are detected through screening programs based on nucleic acid amplification testing (NAAT), antigen detection by ELISA, and DNA hybridization. Screening is useful for identifying asymptomatic infected individuals and in confirming symptomatic infections, but the delay in obtaining results means that initial diagnosis will be primarily based on clinical presentation. Traditional diagnostic techniques used for bacterial infections, culture and Gram stain, are of limited value for chlamydial infections. *Chlamydia* is an intracellular pathogen that requires tissue culture to propagate and so this approach is infrequently used even in developed countries. The unique cell wall structure of Chlamydia makes it very difficult to stain, although it is considered Gram negative. Direct fluorescent antibody staining can identify *Chlamydia* in clinical specimens but is not widely available. Where testing is available, all sexually active young adults under 25 years should be screened for *Chlamydia*. All pregnant women should be screened for *Chlamydia* as well.

5.4 Treatment

The recommended regimen for treatment of *Chlamydia* infection is azithromycin, 1 g orally in a single dose, or doxycycline, 100 mg orally twice daily for 7 days. Alternative 7 day regimens are 500 mg erythromycin base orally four times a day, 500 mg levofloxacin orally once daily, or 300 mg ofloxacin orally twice daily. The frequency of *Chlamydia* and

gonococcal co-infection is high in many locales and dual treatment should be considered. The recommended treatment for LGV is doxycycline 100 mg orally twice a day for 21 days or alternatively, erythromycin base, 500 mg orally four times a day for 21 days. Azithromycin, 1 g orally once weekly for 3 weeks, may also be effective but clinical data is lacking. LGV buboes may require aspiration.

6. Gonorrhea

Neisseria gonorrheoae is an intracellular Gram-negative aerobic diplococcus that is the causative agent of gonorrhea. The adjacent sides of the diplococci pairs are flattened giving a characteristic kidney bean shape. Gonococci initially penetrate mucosal columnar epithelial cells and pass thru to establish infection in the subepithelial space. Cell destruction mediated by gonococci and the host inflammatory response is responsible for the disease pathology. Gonococci frequently change their surface antigens and lasting immunity does not develop. Therefore, re-infection is common.

6.1 Epidemiology

Gonorrhea is the second most common bacterial STI in the world with 62 million cases annually and is most prevalent in south and Southeast Asia with 27 million cases annually, and sub-Saharan Africa with 17 million cases annually. Gonococcal infection is most common among young persons, particularly those 15-24 years old. Women have a 60-80% risk of acquiring gonorrhea from a single act of vaginal intercourse with an infected man; men have only a 20-50% chance of acquiring infection from intercourse with infected women. Transmission among men who have sex with men is more efficient than a man's risk during heterosexual sex and gonorrhea prevalence is several fold higher in this demographic group. Pharyngeal and rectal gonococcal infection is also especially prevalent in this group. Co-infection with *Chlamydia* is common, occurring in up to 50% of gonococcal infections in some countries.

6.2 Clinical manifestations

Symptoms of infection in men usually appear 2-5 days after exposure with a range of 1-30 days. Women are less likely to have symptomatic infection, up to 70% are subclinical, but those who develop symptoms do so within 10 days of infection. The majority of men with gonococcal infection develop urethritis with a white, yellow, or greenish urethral discharge, dysuria, and sometimes painful and swollen testes. Erythema of the meatus is sometimes observed. Non gonococcal urethritis is usually characterized by less purulent and less copious discharge with little erythema of the meatus. The endocervical canal is the primary site of infection in women. Females with endocervicitis and urethritis experience dysuria, a purulent vaginal discharge, pelvic pain, and pain and bleeding brought on by sexual intercourse. Symptoms of rectal infection include itching, mucopurulent discharge, bleeding, tenesmus, and painful bowel movements. Pharyngeal infection is characterized by exudative pharyngitis and cervical lymphadenopathy. Untreated gonorrhea can lead to severe complications in both men and women. Gonorrhea can spread from the cervix and vagina to the fallopian tubes and uterus leading to chronic salpingitis or pelvic inflammatory disease, ectopic pregnancy, and infertility from scaring of the fallopian tubes. Pregnant women may experience chorioamnionitis and septic abortion. In men epididymitis, usually accompanied by unilateral testicular pain and swelling with fever, is

relatively rare but can cause sterility. However a more likely cause of epididymitis in sexually active young men is *C. trachomatis*. Posterior urethritis, urethral stricture and prostatitis in men and Bartholin gland abscesses in women are additional complications of genital infection. In approximately 1- 3% of infected adults, with a higher occurrence in women, gonococci disseminates via the bloodstream to produce characteristic papulopustular lesions, and to infect joints, typically in fingers, wrists, toes, and ankles, causing septic arthritis. These manifestations are accompanied by fever and can range from mild to severe. Other less common complications of disseminated infection include a purulent conjunctivitis from autoinoculation, fatal septic shock, meningitis, perihepatitis, osteomyelitis, rapidly progressing endocarditis, especially of the aortic valve, and adult respiratory distress syndrome. Neonatal gonococcal infections are now an infrequent occurrence in developed countries but remain a serious problem in developing countries. Newborns infected during birth can develop conjunctivitis, known as ophthalmia neonatorum, which may lead to blindness. Neonates can also acquire pharyngeal or rectal infection and, rarely, develop gonococcal sepsis or pneumonia.

6.3 Diagnosis

There are currently five available tests for detection of gonorrhea; Gram stain, culture, nucleic acid amplification tests (NAAT), gonorrhea antigen detection tests, and nucleic acid hybridization tests. Clinical signs and symptoms of cervicitis or urethritis and the presence of Gram-negative intracellular diplococci within polymorphonuclear neutrophils from urethral, or less commonly, cervical discharge, are diagnostic for gonorrhea. The sensitivity of gram stain is very high in symptomatic men with urethritis but less so in infected women and in rectal infection. Stained smears are not recommended for diagnosis of pharyngeal gonococcal infection. Culture on specialized media can be used for urethral, cervical, pharyngeal, and rectal infection. This is the only testing technique that permits determination of gonococcal antibiotic sensitivity. In resource rich countries, diagnosis using very sensitive NAAT, gonorrhea antigen detection tests via immunoassay, and nucleic acid hybridization tests has become widespread. This has permitted screening of at risk populations and self referred testing in developed countries. NAAT tests are the most sensitive, and can be used on urine samples as well, but require hours to days to yield results. Rapid, point-of-care gonorrhea antigen detection tests and nucleic acid hybridization tests are in use, but are relatively expensive for settings in developing countries. Both of these tests are less sensitive than NAAT and are primarily designed for testing with cervical and urethral material. Some available NAAT, gonorrhea antigen detection tests, and nucleic acid hybridization tests can detect both *N. gonorrhoeae* and *Chlamydia* in the same sample and the NAAT test can be combined with Pap smears.

6.4 Treatment

The recommended treatment for gonococcal infections is ceftriaxone in a single 250 mg dose administered intramuscularly (IM). If unavailable cefixime, 400 mg orally in a single dose, or a single dose injectible cephalosporin plus azithromycin, 1 g orally in a single dose, or doxycycline, 100 mg orally twice a day for 7 days, may be used. Resistance to oral third generation cephalosporins has emerged recently and has been reported throughout Asia and in Australia and some European countries. The recent emergence in Japan of a strain, H041, which is extremely resistant to all cephalosporin-class antibiotics will pose a considerable public health challenge as this strain spreads throughout Asia and beyond.

Therapeutic use of sulfonamides, penicillin, erythromycin, and fluoroquinolones has been largely discontinued due to the development of widespread resistance to these agents. Azithromycin, 2 g orally, is effective but concerns over the prior ease of development of macrolide resistance in *N. gonorrhoeae* should limit its use to special circumstances. Gonococcal infections of the pharynx are more difficult to eliminate and are treated with ceftriaxone, 250 mg IM in a single dose, plus azithromycin, 1 g orally in a single dose, or doxycycline, 100 mg orally twice a day. Neonates born to infected mothers are given erythromycin ointment to the eyes to prevent blindness. Patients infected with *N. gonorrhoeae* are frequently co-infected with *Chlamydia*, and additional treatment for this infection may be appropriate, dependent on local prevalence of these STIs.

7. Syphilis

Treponema pallidum, a thin (0.1-0.18 μm by 6-15 μm) flagellated spirochete, is the etiologic agent of syphilis. *Treponema* spirochetes invade mucous membranes or penetrate through breaks in the skin. Although syphilis is typically acquired via sexual contact the disease can also be transmitted transplacentally and by exposure to blood or lesion exudates from infected persons in the primary and secondary stages of disease.

7.1 Epidemiology

Prior to the antibiotic era, syphilis was a very prevalent disease, particularly in large urban areas. Since then, the incidence has been steadily declining but there are still 12 million new cases each year around the world. Unlike many other STIs, the incidence of syphilis is higher in older individuals and is highest in men aged 30-45. Globally, congenital syphilis is a significant problem and it is estimated that neonatal mortality from syphilis exceeds that of neonatal tetanus, neonatal HIV infection, and mortality from malaria in pregnancy. There is no lasting immunity to syphilis and patients can be re-infected.

7.2 Clinical manifestations

Syphilis presents a wide spectrum of clinical manifestations as it progresses through the different stages of the disease: primary, secondary, latency, and tertiary. Syphilis, particularly the secondary stage, mimics many other infections and has been given the moniker, the "great imitator". The primary stage of syphilis is usually characterized by the appearance of a single sore (chancre) at the site of syphilis entry, although multiple lesions can be present. The chancre appears 10-90 days after infection, approximately 2-3 weeks on average. The chancre is typically a firm, round, and painless ulcer, 1-2 cm in size, which is highly infectious and will spontaneously resolve in 1-6 weeks. Chancres can also be present at non-genital sites, the anus, mouth, or perineum. Regional lymphadenopathy that is rubbery, painless, and bilateral is usually present.

Without treatment the systemic skin rash and mucocutaneous lesions of secondary syphilis appear 4-6 weeks after the primary lesion in approximately 25% of patients following dissemination of the disease throughout the body. Occasionally the symptoms of secondary syphilis will occur prior to resolution of the initial chancre. The red macropapular rash is symmetrical, non-pruritic, and present throughout the body including the palms of hands and soles of feet and may lead to hair loss. White, patchy, raised lesions on mucocutaneous surfaces, known as condylomata latum may also be present. The rash and lesions are accompanied by fever, malaise, and generalized lymphadenopathy. Rare

manifestations of secondary syphilis include hepatitis, glomerulonephritis, and keratitis. Neurosyphilis can occur at any stage of syphilis but is classically associated with tertiary syphilis. Clinical manifestations of early neurosyphilis include acute syphilitic meningitis that typically involves cranial nerves III, VI, VII and VIII; or meningovascular syphilis, a stroke-like syndrome with seizures. Secondary syphilis is usually the fist clinical presentation in persons practicing receptive vaginal or anal intercourse as the primary lesions are often not noticed.

Whereas some secondary syphilis can spontaneously resolve, if untreated, approximately two thirds of secondary syphilis cases enter into a prolonged period of latency where symptoms of infection are absent. Relapses of secondary symptoms may occur in up to 25% of untreated patients, usually within the first year of infection. The latent stage can last for up to 25-30 years but if untreated, about one third of latent infections will progress to tertiary syphilis. Tertiary syphilis is rare in developed countries due to early diagnosis and treatment of syphilis. Tertiary syphilis is characterized by destructive lesions known as gummas, neurologic involvement, and cardiovascular lesions. Gummas, are highly destructive granulomas, usually in the skin, bone and mucosal areas but are sometimes found in other tissues such as genitals, lung, stomach, liver, spleen, spinal cord, breast, brain, and heart. Onset is 10-15 years after infection. Cardiovascular syphilis generally appears about 20-30 years after infection when lesions in the cardiac vasculature produce ascending aortic aneurysm, aortic insufficiency, or coronary ostial stenosis. In tertiary neurosyphilis focal endoarteritis in the blood vessels of the brain and spinal cord provokes signs and symptoms, usually decades after infection, which may resemble other neurologic diseases. Clinical manifestations typically include general paresis and tabes dorsalis. The presence of oral syphilitic lesions is common, particularly in primary and secondary syphilis, and in regions with a high prevalence of syphilis other health care workers, such as dentists, need to be aware of this risk.

7.3 Congenital syphilis

Worldwide each year over 2 million pregnant women, 1.5% of all pregnancies, test positive for syphilis. *Treponema* spirochetes can cross the placenta to infect the fetus resulting in severe adverse pregnancy outcomes. Untreated maternal syphilis will result in stillbirth, premature birth, neonatal death, or congenital infection in up to 80% of pregnancies in developing countries. An estimated 25% of all stillbirths and 11% of neonatal deaths in developing countries are due to fetal syphilis exposure. Symptoms of early congenital syphilis in children less than 2 year old include cutaneous and mucocutaneous lesions, macropapular rash, hepatosplenomegaly, lymphadenopathy, bone alterations from osteitis and osteochondritis, meningitis, pneumonia, and testicular masses. Hematologic abnormalities such as thrombocytopenia and anemia may occur. Early congenital syphilis is more common than late congenital syphilis. Late congenital syphilis in children >2 year old is characterized by Hutchinson's triad, Saddle nose, and bone deformations such as Saber shins. Hutchinson's triad includes tooth deformations where the crown of the incisors is wider in the cervical portion than at the incisor edge and a crescent-shaped notch is present at the incisor edge, interstitial keratitis which can lead to blindness, and eighth nerve deafness. Saddle nose refers to collapse of the bridge and resulting dorsal depression due to erosion of septal support, giving a saddled appearance. Saber shin is a malformation of the tibia with sharp anterior bowing. Interstitial keratitis is the most common manifestation of

late congenital syphilis. These adverse pregnancy outcomes can be prevented by syphilis screening to identify and treat maternal infections prior to 24 weeks gestation.

7.4 Diagnosis

Initial diagnosis of syphilis is typically based on clinical presentation. *Treponema* spirochetes are Gram negative but they cannot be visualized using conventional light microscopy. Darkfield microscopy and direct fluorescent antibody test of spirochetes from lesion exudates and tissue provide definitive diagnosis of early syphilis. These tests however are not utilized in most settings. Presumptive diagnosis of syphilis relies on two types of testing for antibody in blood serum or cerebrospinal fluid. The Venereal Disease Research Laboratory (VDRL) and Rapid Plasma Reagin (RPR), Toluidine Red Unheated Serum (TRUST), and Unheated Serum Reagin (USR) tests utilize a non-treponemal antigen. The VDRL and RPR tests are the most widely used of these. VDRL and PRP testing is most sensitive in the middle stages of the disease, early syphilis and late stage disease may be missed. Detectable antibody titers are not attained until 1-4 weeks after appearance of the chancre and titers often decline to undetectable levels in latency. Non-treponemal tests are nonspecific and can give false-positive results and occasionally false negative results under conditions of antibody excess which can occur during secondary syphilis. Positive results are confirmed with a test utilizing treponemal antigens, such as the fluorescent treponemal antibody absorbed (FTA-ABS) test, treponemal enzyme immunoassay (EIA), microhemagglutination assay for *T. pallidum* antibodies (TPHA), and direct fluorescent antibody-*T. pallidum* test (DFA-TP). These tests are more sensitive than non-treponemal tests in detecting primary and tertiary syphilis. Non-treponemal test antibody titers usually correlate with disease activity and become non-reactive with time after treatment. Treponemal test antibody titers do not correlate disease activity and most (75-85%) will remain reactive for the rest of their lives. Commercially available point-of care tests for syphilis have been introduced recently although these are too expensive for most situations in the developing world.

7.5 Treatment

Benzathine penicillin G, 2.4 million units by intramuscular injection (IM) in a single dose for adults or 50,000 units/kg IM for children, is the preferred treatment for primary, secondary, and early latent stage syphilis. Alternatively, procaine penicillin at 1.2 million units IM daily for 10 days is used. Penicillin allergic non-pregnant patients may be treated with doxycycline, 100 mg orally twice daily for 2 weeks or tetracycline, 500 mg orally four times daily for 2 weeks. Penicillin allergic pregnant patients may receive erythromycin, 500 mg orally, 4 times daily for 14 days. Late latent stage syphilis and tertiary syphilis is treated with three doses benzathine penicillin G at 1 week intervals, 2.4 million units IM each dose for adults and 50,000 units/kg for children. Alternatively, procaine penicillin at 1.2 million units IM daily for 20 days is used. Penicillin allergic non-pregnant patients with late latent stage or tertiary syphilis may be treated with doxycycline, 100 mg orally twice daily for 4 weeks or tetracycline, 500 mg orally four times daily for 4 weeks. Penicillin allergic pregnant patients may receive erythromycin, 500 mg orally 4 times daily for 4 weeks. Neurosyphilis is treated with intravenous aqueous crystalline penicillin G, 3-4 million units every 4 hours (18-24 million units per day) for 10-14 days, or with daily IM injections of procaine penicillin, plus 500 mg probenecid orally 4 times daily, both for 10-14 days. Penicillin

allergic non-pregnant patients with neurosyphilis are treated with doxycycline, 200 mg orally twice daily for 4 weeks or tetracycline, 500 mg orally four times daily for 4 weeks. Non-penicillin allergic pregnant women diagnosed with syphilis are treated with penicillin according to the stage of infection. Early congenital syphilis should be treated with intravenous aqueous crystalline penicillin G at 50,000 units/kg/dose every 12 hours for the first 7 days and every 8 hours for the next 3 days. Alternatively early congenital syphilis is treated with IM injections of procaine penicillin at 50,000 units/kg daily for 10 days. Late congenital syphilis is treated with intravenous or intramuscular aqueous crystalline penicillin G at 50,000 units/kg/dose every 4-6 hours for 10-14 days. For penicillin allergic children, after the first month of life, administer erythromycin, 7.5-12.5 mg/kg orally, 4 times daily for 4 weeks.

8. Chancroid

Haemophilus ducreyi, a fastidious Gram-negative facultative anaerobic coccobacillus, is the causative agent of chancroid. Chancroid is transmitted by vaginal, anal, or oral sex with an infected individual. The organism enters thru breaks in the epithelium and resides primarily in the extracellular spaces. *Haemophilus ducreyi* can resist phagocytosis and untreated lesions may take months to heal.

8.1 Epidemiology

Globally, chancroid is the most common cause of genital ulcer disease in regions where the disease is endemic. WHO estimates the annual global incidence to be about 6 million cases. Chancroid occurs in parts of Africa, south-east Asia and the Caribbean where it accounts for 23-56% of genital ulcer disease. Chancroid is more common in men than women and more common in areas where HIV prevalence is high (>8%). The incidence of chancroid is much lower in developed countries and sporadic outbreaks there are associated with travel, prostitution, and drug use. Chancroid, as are all genital ulcer producing STIs, is a risk factor for HIV transmission.

8.2 Clinical manifestations

After an incubation period of several days to two weeks, a tender erythematous papule develops at the site of inoculation which progresses to a pustular stage. The pustle ruptures within 2-3 days to form a painful genital ulcer with soft edges. Chancroid ulcerative lesions vary from 3-50 mm across but are typically 10-20 mm. Chancroid ulcers can be irregular, round, or oval in shape, are sharply circumscribed with an undermined edge, and contain a grey or yellow purulent exudate. Lesions will have a surrounding cutaneous erythema. One half of men have only a single ulcer and lesions typically appear on the penis: penile shaft, coronal sulcus, prepuce, urethral meatus, and glans. In women infection is often subclinical. Women have multiple ulcers more frequently than men that may merge to form large ulcers. Ulcers in women occur on the fourchette, labia majora, labia minora, cervix, perianal region, and inner thighs. “Kissing ulcers” may develop on the skin surfaces apposing the initial ulcer. Women may also experience dysuria and dyspareunia. Rectal sores in men or women may bleed or cause pain during defecation. Buboes, swelling of the inguinal lymph nodes, occur in one third to one half of infected individuals 1-2 weeks after the ulcers form and these may rupture, producing draining abscesses. The development of buboes is a more

common occurrence in men than women. Buboes are painful, tender, and fluctuant with underlying erythema, and are typically unilateral. Supperative adenopathy is almost pathognomonic for chancroid. The skin over the bubo does not become thickened and edematous or show furrows as in the adenopathy of LGV. Chancroid can also spread via self inoculation to other anatomical sites. Chancroid in HIV-infected patients may produce a larger number of ulcers, atypical ulcers, extra-genital lesions, and longer lasting ulcers even with treatment.

8.3 Diagnosis

Definitive diagnosis of chancroid requires cultivation of *H. ducreyi* on special culture media, which is not routinely carried in most laboratories. Culture on two media is recommended as not all *H. ducreyi* strains can be cultured using one medium. Culture also requires a humid environment, 5% CO_2, and incubation at 33-35 ^oC. Swabs for culture are collected from the undermined edge of the ulcer and the fastidious nature of *H. ducreyi* necessitates use of transport media if the organisms are not cultured within a few hours. Presumptive diagnosis by microscopy is possible if the organism load in ulcers is high and Gram-negative coccobacillus arranged in chains, paired chains or aggregates ("school of fish" appearance) are visualized. However the value of microscopy for diagnosis is limited by low sensitivity and specificity of this technique. Aspirates from buboes are less likely to yield positive results on microscopy or culture. In many cases chancroid is diagnosed clinically and treated without a definitive diagnosis. The combination of painful genital ulcer and suppurative inguinal lymphadenopathy is also supportive of a diagnosis of chancroid. Nucleic acid amplification tests for diagnosis have been developed but are not widely available.

8.4 Treatment

Azithromycin (1 g orally) or ceftriaxone (250 mg IM) offer the advantage of single-dose therapy. Alternatively ciprofloxacin (500 mg orally twice daily for 3 days) or erythromycin base (500 mg orally three times a day for 7 days) may be used. For reasons of cost, erythromycin is usually used for treatment in developing countries. Isolates with intermediate resistance to ciprofloxacin or erythromycin have been reported but data are rather limited on the current status of *H. ducreyi* drug resistance. Ulcerative lesions should be kept clean to avoid the chance of secondary infections. Fluctuant lymph nodes can be aspirated through healthy skin. Incision and drainage or excision of nodes may delay healing. Uncircumcised men and HIV-positive patients may not respond as well to treatment. Large ulcers may require weeks to resolve after treatment and patients should be followed until there is clear evidence of improvement or cure.

9. Human papilloma virus

Human papillomavirus (HPV) is a member of the papillomavirus family of viruses that infect only humans. HPVs can be divided into two general groups based on their preferred infection site: cutaneous and mucosal. Genital HPV, a member of the mucosal HPVs, is transmitted through sexual contact and infects the anogenital regions. There are more than 40 types of HPV that infect the genital area. Non-oncogenic or low risk HPV types are the causative agents of genital warts and recurrent respiratory papillomatosis. Oncogenic or high risk HPV types are the cause of cervical cancers and are associated with other anogenital cancers in men and women.

9.1 Epidemiology

Genital human papillomavirus is considered to be one of the most prevalent STIs in the world. It is estimated that more than 50% of sexually active individuals become infected at least once in their life. WHO estimates that 14.3% of women in developing regions and 10.3% of women in developed regions with normal cervical cytology are infected with HPV. Incidence of HPV in women increases significantly with severity of abnormal cervical cytology. Prevalence of HPV reaches to greater than 70% in women with cervical cancer.

9.2 Clinical manifestations

Asymptomatic genital HPV infection is common and usually self-limited. Seventy percent of infections are gone in 1 year, and 90% in 2 years. The most common symptom of genital HPV infection is genital warts, also known as condylomata acuminata. Genital warts appear as a small white bump or groups of bumps in the genital area. Genital warts are usually flat, papular, or pedunculated growths. However, they can be small or large, raised or flat. Genital warts are usually themselves asymptomatic, but can sometimes be painful and pruritic, depending on the size and anatomic location. Growths commonly occur around the introitus in women, under the foreskin of the uncircumcised penis, and on the shaft of the circumcised penis. Genital warts can also be found in or on the cervix, vagina, urethra, perineum, perianal skin, and scrotum. Intra-anal warts are most often observed in individuals who have had receptive anal intercourse, but may be present in men or women with no history of anal sexual contact.

9.3 Health sequelae

The correlation between persistent HPV infection and cervical cancer has been well established. Cervical cancer is the 2nd most common cancer among women, worldwide. Eighty-six percent of these cases occur in developing countries, making up 13% of the world female population. There is now increasing evidence linking HPV to anogenital cancers other than cervical cancer. These include anal, vulvar, vaginal, penile, and head and neck cancers. Anal cancer occurs rarely with about 99,000 cases in 2002, sixty percent of cases occurring in women and 40% in men. This type of cancer is more prevalent in populations of men who have sex with men and HIV-positive populations. Vulvar cancers make up about 3% of the gynecological cancers, with 40% of them occurring in developing countries. The majority of these cases occurring in the developed world suggest that HPV screening may not be an effective preventative method. Vaginal cancers make up 2% of gynecological cancers, with a majority of vaginal cancers (68%) occurring in developing countries. Penile cancer represents 0.5% of cancers in men. In western countries, incidence if penile cancer in men is less than 1 per 100,000, however, this rate increases in Latin America, India, and Thailand. Two-thirds of oral cancers occur in developing countries and about 15-20% of oral cancers are associated with HPV infection. Growing evidence suggests that HPV-related oral pharyngeal cancers are associated with the practice of oral sex.

9.4 Diagnosis

The presence of genital warts is a straight forward method for diagnosis of HPV. However, in the case of asymptomatic infections, there is no general diagnostic test used to screen normal patients for HPV. The Papanicolaou test (Pap smear or Pap test) is a cytological examination of cervical tissue sample that is used to screen for cervical cancer or

precancerous lesions. The Pap smear is more commonly used in developed countries. Abnormal results for a Pap smear usually result in screening of the tissue sample for the presence of HPV DNA. HPV DNA testing has been shown to have a higher sensitivity than cytology and a high negative predictive value for detecting cervical precancerous lesions. Other diagnostic strategies include visual inspection with acetic acid (VIA), self-vaginal sampling, and liquid based cytology (LBC). VIA has shown sensitivity similar to that seen with cytology, but has a lower specificity, which could lead to over treatment. However, its use has shown a decrease in the incidence of and mortality from cervical cancer, and may therefore be a useful method in resource poor areas. Developing countries have attempted to implement HPV screening programs with variable success. Successful implementation of these programs in some countries such as Taiwan, Japan, Singapore, and developed African countries has caused a decline in incidence and mortality of cervical cancer. In the remainder of the developing world either no screening programs currently exist or screening has had little success due to poor infrastructure and competing health priorities in these countries.

9.5 Treatment

Treatment is not recommended for subclinical genital HPV because these infections typically clear spontaneously. However, there are treatments for the diseases that are caused by HPV infection. Genital warts can resolve themselves or be removed by patient-applied or provider-administered therapy. Patient-applied therapy recommended by the CDC consists of podofilox 0.5% solution or gel, imiquimod 5% cream, or sinecatechins 15% ointment. Provider-administered therapy is cryotherapy with liquid nitrogen or cryoprobe applications ever 1-2 weeks, 10-25% podophyllin resin in a compound tincture of benzoin, 80-90% trichloroacetic acid (TCA) or bichloroacetic acid (BCA), or surgical removal by tangential scissor excision, tangential shave excision curettage, or electrosurgery. No evidence suggests that one treatment regimen is better than the other. Treatment against cervical lesions includes removal of precancerous lesions using cryotherapy and continuous preventative screening of cervical tissue.

A preventive strategy based on the development of vaccines against HPV is now widely available across the globe. A quadrivalent vaccine, Gardasil (Merck Co.) protects against 2 types of HPV that cause 75% of cervical cancer (HPV 16 &18) and the 2 types of HPV that cause 90% of genital warts (HPV 6 & 11). Gardasil can be used for both males and females ages 9-26. This vaccine is given in a series of 3 0.5 mL intramuscular injections at 0, 2, and 6 months. A bivalent vaccine, Cervarix (GlaxoSmithKline), protects against HPV 16 & 18 and is only approved for women ages 10-25. This vaccine is given in a series of 3 intramuscular 0.5 mL doses at 0, 1, and 6 months. Many countries have developed their own individual vaccine schedules. Both vaccines have been shown to be highly immunogenic and effective in prevention of incidence and persistent HPV infections that could lead to the development of precancerous lesions. It is recommended that vaccination begin at ages at which individuals have not yet become sexually active.

10. Herpes

Genital herpes is caused by herpes simplex viruses type 1 (HSV-1) or type 2 (HSV-2) with HSV-2 the primary genital STI. HSV-1 is acquired orally, usually in childhood, and typically

causes cold sores and sometimes keratitis. HSV-1 can also cause genital infection but recurrent episodes during infection with HSV-1 are much less frequent. HSV-1 and HSV-2 are typically transmitted during sexual contact by virus shed from herpes sores but virus can also be released intermittently between outbreaks from skin without apparent sores. Herpes virus enters through mucous membranes or breaks in the skin and replicates locally in mucosal epithelial cells. Between outbreaks the herpes virus ascends peripheral sensory neurons to the dorsal root ganglia and becomes latent.

10.1 Epidemiology

Herpes is the most common STI in the world and HSV-2 infection is the main cause of genital ulcers in developing countries. An estimated one sixth to one third of the world's population has genital herpes caused by HSV-2. HSV-2 prevalence is greater than 60% in sub-Saharan Africa and East Asia and between 25-40% in Latin America, Eastern Europe, South Asia, and South-east Asia. HSV-2 prevalence rates are less than 20% in North America and Western Europe and below 10% in North Africa, the Middle East, Japan, Australia and New Zealand. Most herpes infections are asymptomatic and herpes is usually spread by people who are unaware they have the disease. Symptomatic genital herpes infection is approximately twice as common in women as in men. Transmission from an infected male to a female partner is more likely than transmission from infected female to a male partner during vaginal intercourse. Rates of herpes infection are also higher in men who have sex with men and in HIV-positive individuals. Herpes seroprevalence rates are as high as 80% among HIV-positive populations in North America, Europe and Africa.

10.2 Clinical manifestations

Most individuals have no or only minimal symptoms from herpes infection and do not realize they are infected. Herpes appears 2-7 days after infection as small, pruritic and painful, usually multiple, grouped vesicles (blisters) with a red base on or around the genitals and rectum or on the buttocks or thighs. The vesicles will ulcerate to leave shallow lesions that heal in 2-4 weeks. During the initial episode additional groups of sores may appear. Fever, malaise, and bilateral inguinal lymphadenopathy that is firm and tender may also be present. Infection in women usually involves the vulva, vagina, and cervix. In men lesions usually appear on the glans penis, prepuce, or penile shaft. After resolution of the primary infection herpes enters a latent state. However, outbreaks will re-occur from weeks to months after the initial infection, particularly during periods of stress or illness, and typically 4 or 5 outbreaks occur within the first year. About one half of patients experience prodromal symptoms of tingling or pain at the eruption site 1-2 days prior to the appearance of lesions. Although herpes infection persists indefinitely outbreaks diminish in number and severity with time. The duration and intensity of outbreaks are usually more severe in persons with suppressed immune systems. Persons with immune deficiencies such as HIV-infected persons may have persistent, extensive, and severe mucocutaneous lesions involving large areas of perianal, scrotal, or penile skin. Complications of herpes infection include an aseptic meningitis in as many as 10% with primary infection, transverse myelitis, and perinatal transmission. Pregnant women experiencing primary genital herpes during birth can transmit a potentially fatal herpes infection to their infant and a caesarean delivery may be appropriate in these cases. The risk of transmission during birth is very low in women with recurrent disease. Infected neonates can experience disseminated disease with

organ failure, severe neurologic damage, ocular involvement, cutaneous and mucocutaneous sores, and even death.

10.3 Diagnosis

There are four types of testing employed in herpes diagnosis, DNA testing, antibody testing, antigen testing, and herpes culture. Nucleic acid amplification tests are very sensitive and can detect herpes DNA in samples from herpetic sores even when virus is in low copy number, such as in older lesions or in cerebrospinal fluid samples. It is the method of choice to detect HSV meningitis, encephalitis, and keratitis. HSV antibody tests are available to measure both IgM antibody, which can detect primary herpes infection after first several days of infection, and IgG antibody, which indicates prior HSV infection. The presence of HSV-2 antibody indicates anogenital infection but the presence of HSV-1 antibody does not distinguish genital infection from oral infection. Rapid antibody tests are available that detect antibodies to HSV-2 in blood from a finger stick within 10-15 minutes. The relatively quick turnaround and ease of this antibody tests makes it ideal for herpes screening for persons with undiagnosed disease as well as disease diagnosis. Fluorescently labeled antibody is used in antigen tests to detect markers expressed on herpes infected cells. Herpes culture is very specific but prone to false negative results, especially for recurrent infection, and requires several days to a week for results. Material from the base of the ulcer in fresh primary lesions is best for any herpes diagnosis as viral shedding decreases as lesions age and heal and in subsequent outbreaks. However, the requirement for tissue culture of host cells to grow herpes limits the utilization of this technique. Herpes can also be diagnosed by visual examination for the characteristic vesicles and sores although signs and symptoms of herpes can vary, making diagnosis problematic in some patients.

10.4 Treatment

There is no effective treatment for genital herpes but antiviral medications can lessen the duration and severity of outbreaks. Antiviral prophylaxis also reduces the chances of transmission from infected individuals to uninfected partners. Clinical episodes can be treated by acyclovir in a 7 day regimen for the initial episode or a 5 day regimen for subsequent episodes at 200 mg orally 5 times daily or 400 mg orally 3 times daily. Ideally treatment should begin within one day of the appearance of the herpes vesicles. Suppressive therapy uses acyclovir, 400 mg orally twice daily, continuously. Alternatively the acyclovir analogues valaciclovir and famciclovir can be used for treatment and prophylaxis although the dosages and regimens may vary. The acyclic nucleoside drugs are effective and well tolerated in most patients. Immunosuppressed individuals such as HIV-positive patients may respond poorly to treatment and require larger doses and longer treatment schedules or even parenteral drug administration.

11. Granuloma inguinale (Donovanosis)

Calymmatobacterium granulomatis is an intracellular Gram-negative facultative aerobic coccobacillus that is the causative agent of granuloma inguinale. Other designations for this disease include granuloma venereum and donovanosis, named for the discoverer of the infectious agent. A close phylogenetic relationship with *Klebsiella* spp. has led some to call for a reclassification of *Calymmatobacterium* into the genus *Klebsiella*. Some *C. granulomatis*

strains are capsulated. *Calymmatobacterium granulomatis* resides in the cytoplasm of mononuclear phagocytes or histiocytes in tissue.

11.1 Epidemiology

The incidence of granuloma inguinale has decreased in recent years but it still endemic in certain tropical and subtropical regions; south-east India, Indonesia, Papua New Guinea, South Africa, Guyana, Peru, Argentina, Brazil, and among aborigines of Central Australia. It is only occasionally reported in developed countries. Most infections occur in sexually active people 20-40 years of age and men are more than twice as likely to have disease. Granuloma inguinale is spread primarily thru vaginal or anal intercourse, infection via oral sex is rare. Non-sexual transmission via contact with infected material from lesions or by fecal contamination is possible.

11.2 Clinical manifestations

The infection begins approximately 10-50 days after exposure with the appearance of small, relatively painless, erythematous pustules or subcutaneous nodules. These will ulcerate to produce shallow and sharply demarcated lesions. Four types of lesions are described: ulcerogranulomatous ulcers, the most common, oozing lesions with a beefy red friable base that bleeds when touched, hypertropic ulcers with a raised irregular edge, sometimes completely dry, deep necrotic ulcers with an offensive smell from decaying tissue, and sclerotic ulcers with fibrous and scar tissue. In early stages the ulcers resemble chancroid, in later stages granuloma inguinale may resemble LGV. The lesions slowly expand destroying adjacent tissue. Anatomical areas most commonly infected in men include the sulcus, subprepucial region, and the anus. Women are most affected in the labia minor, fourchette, and occasionally in the cervix and upper genital tract. Extra-genital lesions occur in a minority of patients, these are secondary to the genital lesions. Oral lesions are the most frequent, loss of teeth indicates oral bone involvement, but lesions are possible on any surface. Very rarely disseminated donovanosis may occur, spreading to cause lesions in the liver, other organs, and bone, particularly tibia. Disseminated disease may be fatal as a diagnosis of donovanosis is rarely considered. Inguinal lymphadenopathy is generally absent. Untreated disease results in the destruction of genital tissue with scarring.

11.3 Diagnosis

Granuloma inguinale is diagnosed by clinical signs, particularly the presence of persistent spreading lesions, and the demonstration of intracellular Donovan bodies in the cytoplasm of mononuclear phagocytes or histiocytes present in scrapings or punch biopsies stained with Giemsa, silver, or Wright's stain. Specimens from just below the surface of the ulcer are most likely to yield positive results. Culture is difficult to perform as it requires growth of host cells and is not readily available.

11.4 Treatment

WHO guidelines recommend azithromycin, 1 g orally followed by 5500 mg daily or doxycycline, 100 mg orally twice daily but do not state the duration of therapy. Typically therapy is given for 3-6 weeks or until lesions are healed. Alternative regimens are erythromycin, 500 mg orally 4 times daily or tetracycline, 500 mg orally 4 times daily or trimethoprim 80 mg/sulfamethoxazole 400 mg, 2 tablets orally twice daily for a minimum

of 14 days. WHO recommends the addition of a parenteral aminoglycoside, such as gentamicin, for the therapy of HIV-positive patients. Treatment should be continued until complete healing is achieved. The intracellular residence of *C. granulomatis* makes it somewhat resistant to treatment.

12. STIs among travelers and immigrants from the tropics

Travel is known to be a major factor in the spread of STIs around the world, particularly in developing countries where STIs are endemic and very high rates are encountered in commercial sex workers. The rapid spread of antibiotic resistance around the world for a number of STIs and the spread of HIV infection are cases in point. It is difficult to assess the risk of acquiring STIs during travel in which sexual acts occur. Poverty and lack of legal enforcement certainly facilitate access to sexually compliant individuals in the developing world. In addition, risk-taking behavior increases when on vacation and often vacations involve higher risk activities than the traveler typically encounters at home. Studies have shown that engaging in sexual activity is the specific reason for travel, i.e. 'sex vacations', in some travelers. Reports of lower condom rate usage and higher rates of engagement in anonymous sex by travelers support a conclusion of increased risk. Travel clinics and physicians advising overseas travelers should counsel travelers about the risks and proper prophylactic regimens available. Travelers should also be strongly encouraged to be tested for STIs upon return if they have engaged in sexual activity. There are high rates of asymptomatic infection for many STIs and long incubation periods can also occur before there is an onset of symptoms. Immigrants and refugees pose a problem to the health care system in developed countries as well. STIs uncommon in the developed world such as chancroid, LGV, and donovanosis present a diagnostic challenge to the physician unfamiliar with these diseases. Incorrect diagnosis and subsequent incorrect treatment can delay resolution of the disease and increase the risk to the patient and sex partners, even permitting local mini-epidemics of new STIs. Health care providers should be aware of uncommon STIs present in their patient's country of origin when evaluating symptoms of genital infection in this population.

13. Prevention and control

Prompt diagnosis and treatment of infected individuals and public education of sexually active populations on proper prevention and prophylactic measures for STIs are the foundation of STI prevention and control. To be successful this approach should be supplemented with screening programs to identify individuals with subclinical infections as many, if not most, STIs are transmitted by individuals who do not know they are infected. However, the lack of adequate diagnostic capacity in most tropical settings severely compromises diagnosis and screening for STIs. This is the biggest barrier to addressing the STI epidemic in the developing world. Provision of a minimal diagnostic capacity, both equipment and trained individuals, at the initial point of contact with STI patients would yield enormous benefits. The development of affordable point-of care tests for STIs would also significantly advance efforts for controlling STIs in these countries. Public health education initiatives for STIs should encourage safe sex behavior and emphasize the advantages of prompt access to healthcare for suspected infections. Education is key to changing sexual behavior in high risk groups, especially adolescents and young adults who

are disproportionately afflicted by STIs. Some health care advisors have advocated a policy of treating all sexually active adolescents and adults in a village or locale as a means to controlling STIs, an approach similar to mass treatment with anti-helminthics utilized to control the endemic of intestinal worm disease. This approach may be the single most cost effective mechanism for managing the STI epidemic in developing countries and should be given careful consideration. Although perhaps not applicable for all STIs, certainly for highly prevalent STIs with drugs that are inexpensive, safe, efficacious, and well tolerated, such as metronidazole for treating trichomoniasis, this approach has much merit.

On an individual basis the only truly reliable protection is abstinence from sexual activity. People in long term monogamous relationships also have greatly reduced risk of STIs and HIV. Vaccines are available for the prevention of HPV infection and potential HIV vaccines are in clinical trials. Protective measures for sexually active individuals include reducing the number of sexual partners and the use of latex condoms and other barriers during sexual activity. Consistent and proper use of condoms has been shown to reduce the transmission of STIs and HIV. Male circumcision has also been shown to be significantly protective against transmission of HIV and STIs. STI treatment should include sexual partners of the index case whenever possible to prevent re-infection and to reduce disease transmission. Due to compliance issues and difficulties in following patients in many locales, directly observed single dose therapies are preferred for the treatment of STIs.

14. The future: Vaccines for STIs

Vaccination offers the ultimate tool for control of STIs; prevention before exposure. Safe and efficacious vaccines could eliminate the vast majority of STI-associated morbidity and mortality. Unfortunately this goal has only been attained relative to HPV infection (section 9.5) and prospects for additional STI vaccines in the immediate future are remote. In part, this is because the precise correlates of protective immunity have not been well-defined for these STIs. However, some progress has been made in the development of vaccines for genital herpes and *Chlamydia* infection. Three types of herpes vaccines have shown efficacy in animal models: (i) HSV-2 subunit vaccines combined with adjuvant; (ii) gene delivery vehicles, such as vaccinia virus, *Listeria* or *Salmonella typhimurium*, expressing HSV-2 proteins; and (iii) attenuated (replication-defective) HSV-2 viruses. Subunit vaccines based on herpes glycoproteins gD and gB have failed in two human clinical trials. Live attenuated viruses have not been tested in humans to date although they have shown the most promise in animal models. Recent progress in identification of T-cell epitopes mediating asymptomatic versus symptomatic disease manifestation should enhance future development of a herpes vaccine. *Chlamydia* candidate vaccines containing *Chlamydia* major outer membrane protein (MOMP) with HPV major capsid membrane protein L1, recombinant MOMP with cholera toxin, co-expressed *Chlamydia* Porin B and polymorphic membrane protein-D proteins in a *Vibrio cholerae* ghost delivery system, MOMP-based DNA vaccines, and live attenuated *Chlamydia* organisms have each shown efficacy in animal models but none have advanced to human trials.

Although the lack of progression to disease in some individuals infected with gonorrhea, syphilis, chancroid, and granuloma inguinale and the ability of immune responses to contain and clear infections in others in the absence of treatment indicates the theoretical feasibility of vaccination, progress on the development of a vaccine for these STIs has lagged. The syphilis spirochete, *Treponema pallidum*, has a unique molecular architecture and

the cell envelope consists of a dual membrane structure. The outer membrane is poorly immunogenic, lacking lipopolysaccharide and possessing few integral membrane proteins that could serve as surface antigenic targets for the host immune system. The strong antibody response observed in syphilis is principally generated by lipopolysaccharide and protein immunogens located in the inner membrane where they are inaccessible to this antibody response. To date, research on a syphilis vaccine has not progressed past the identification of these rare outer membrane proteins as candidate vaccine antigens. Development of a gonococcal vaccine has been hampered by the ability of *N. gonorrhoeae* to change surface antigens, especially Type IV pili, deficiencies in current animal models, and the lack of target capsular polysaccharides such as are present in *N. meningitidis*. Two candidate gonorrhea vaccines, utilizing killed whole gonococcal cells or pilus and pilus-associated proteins, have been tested in human clinical trials but neither produced protection. Recent work on gonococcal vaccines has been focused on the identification of potential B- and T-cell epitopes for candidate antigens. The relatively low incidence of chancroid and donovanosis in most developed countries is mirrored by limited research interest towards development of vaccines for *Haemophilus ducreyi* and *Calymmatobacterium granulomatis* infections and there is little in the way of published work or progress on vaccines for these organisms.

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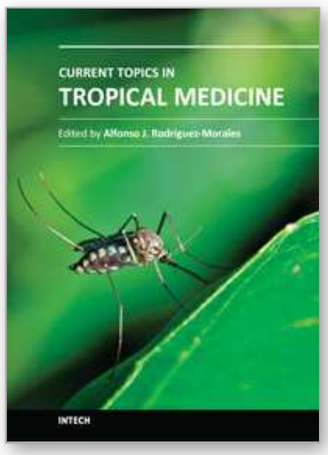

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