Natalie Neu

Sexually Transmitted Diseases

Although the HIV pandemic has alerted many individuals to the risk of sexual activity, there has been no major decline in sexually transmitted disease, which remains a major problem in the U.S. and globally, with complications of untreated STDs including infertility, cervical cancer, and enhanced acquisition of HIV. A full discussion of how to obtain a sexual history and counsel patients on safer sex techniques is not possible during this lecture. A few general principles should be highlighted at the outset:

- Nonjudgmental, open-ended questions help elucidate an accurate sexual history.
- Persons at risk for STDs should be educated and counseled on ways to adopt safer sexual behavior, including education on the correct usage of the male and female condom and their limitations – condoms are likely to be more effective in preventing infections transmitted by fluids from mucosal surfaces (e.g., gonorrhea, chlamydia, and HIV) than in preventing those transmitted by skin-to-skin contact (e.g., HSV, HPV).
- Frequent use of spermicides containing nonoxynol-9 (N-9) has been associated with genital lesions, which may be associated with an increased risk of HIV transmission.
- STD risk factors include young age (under 24 years old, but particularly under 20 years old), multiple sexual partners, history of prior STDs, recent new sexual partner, substance use, and contact with commercial sex workers.
- Patients with one STD often have another STD and should be screened appropriately.
- All patients being evaluated for STDs should be screened serologically for syphilis and offered testing for HIV.
- Treatment of STDs using single dose drug regimens are preferable due to improved compliance and ease of administration. Treatment of STDs may differ in HIV-infected persons.
- Partners of patients with STDs should be evaluated and, when indicated, treated.
- Local and state public health practices including partner notification and disease reporting should be followed.
- Asymptomatic persons who are at risk for STDs should be screened for STDs.

This lecture will concentrate on the bacterial STDs (gonorrhea and chlamydia – syphilis is covered in a separate lecture). The viral STDs HSV and HPV are included here so that we can discuss all the major STDs, but they are covered in more detail elsewhere. HIV is covered in subsequent lectures. Hepatitis A, B, and C, all of which can be sexually transmitted, are covered in the GI section of the course.

Gonorrhea

Gonorrhea is an acute bacterial infection, transmitted by sexual contact or perinatally, which may involve asymptomatic infection, urethritis, cervicitis, pelvic inflammatory disease, and disseminated infections. The etiologic agent is *Neisseria gonorrhoeae*.

Epidemiology

Gonorrhea is second only to chlamydia as the most commonly reported STD in the U.S. An estimated 720,000 new *N. gonorrhoeae* infections occur annually in the U.S. Populations at greatest risk include 15-24 year olds. Transmission may occur from infected urethral, cervical, rectal and pharyngeal surfaces. The incubation period is 1 to 14 days, but usually 2 to 5 days. Transmission from male to female after one exposure is 50-70%, whereas transmission from female to male is 20%. Recurrent infection is common. The single most important axiom about

the epidemiology of this disease is that gonorrhea is usually spread by carriers who have no symptoms or who have ignored symptoms. Symptomatic patients, male or female, have usually been recently infected by such carriers, who must in turn be traced and treated to prevent reinfection. Asymptomatic carriage is more common in women than in men. As many as half of all infected women have mild or asymptomatic infections, whereas most men are initially symptomatic. Pelvic inflammatory disease due to chlamydia and gonorrhea is an enormous public health problem leading to infertility and ectopic pregnancy. In addition, gonorrhea, as well as chlamydia (discussed below) is associated with an increase in the risk for transmission or acquisition of HIV.

Microbiology and Pathogenesis

N. gonorrhoeae is an aerobic non-motile Gram negative coccus that tends to grow in pairs (diplococci) with adjacent sides flattened (kidney bean shaped). It forms oxidase-positive colonies and is differentiated from *Neisseria meningitidis* (the other pathogenic *Neisseria*, which causes meningitis) by its ability to ferment glucose but not maltose. It is a fastidious organism, requiring complex media and a CO_2-enriched atmosphere for growth.

Gonococci primarily infect columnar or cuboidal epithelium. They attach to mucosal epithelial cells, penetrate into the cells and multiply, and then pass through the cells into the subepithelial space, where infection is established. Pili, Porin, and Opa proteins mediate attachment and penetration into host cells. The gonococcal lipooligosaccharide (LOS) stimulates the inflammatory response and release of TNF-α, which causes most of the symptoms associated with gonococcal disease. Vigorous neutrophil response leads to sloughing of the epithelium, development of submucosal microabscesses, and exudation of pus. Some of the virulence factors are described below:

Pili – Gonococci have many pili on their surface that extend through the peptidoglycan and outer membrane. Pili are composed of repeating protein subunits (pilins), whose expression is controlled by the *pil* gene complex. Pili are responsible for tight binding of the bacteria to nonciliated mucosal cells. The tight binding prevents the gonococci from being washed away by vaginal discharge or urine. The presence of pili has also been shown to inhibit phagocytosis by neutrophils. The pili are essential for virulence. Infection was not established in human volunteers inoculated with mutants of *N. gonorrhoeae* lacking pili.

The **Porin** protein is the major outer membrane protein (OMP) in *N. gonorrhoeae* which is necessary for the organism's survival. It forms pores for nutrients to pass into the cell and wastes to exit. The protein can interfere with degranulation of neutrophils and phagolysosome fusion, thus protecting the bacteria from the host's inflammatory response. It also facilitates invasion into epithelial cells and resistance to complement-mediated serum killing.

Opacity proteins (Opa) -- These cell surface proteins, or adhesins, also mediate tight binding to epithelial cells and are important for cell-to-cell signaling.

Immune evasion:

Antigenic variation – Frequent changes in antigens is one of the most prominent features of *N. gonorrhoeae*. A single clone of *N. gonorrhoeae* can give rise to variants expressing different antigenic forms of both pili and Opa proteins, due to multiple copies of the pilin and Opa genes in the *Neisseria* chromosome. This antigenic variation helps the organism survive the host immune response. Antibodies specific for one form of pilin or Opa protein are not effective against another form. Each isolate of the gonococcus may have a unique antigen profile allowing the organism to reinfect a host repeatedly.

Also important in immune evasion is **phase variation**, the ability to switch production of pilin and Opa proteins on or off. The gonococci also secrete an **IgA protease** which cleaves and inactivates the heavy chain of the IgA1 isotype.

Lipooligosaccharide (LOS), similar to the lipopolysaccharide (LPS) seen in other Gram negative bacteria, is an important cell wall component of *N. gonorrhoeae* with endotoxin activity.

Transferrin-binding proteins mediate acquisition of iron for bacterial metabolism by competing with their human hosts for iron (fundamentally different from most bacteria that synthesize siderophores to scavenge iron).

***B*-lactamase** – some strains produce *B*-lactamases that can degrade penicillin, leading to resistance.

Clinical Features

Up to 30% of male and female patients with gonorrhea will also be infected with *Chlamydia trachomatis*. Patients diagnosed with gonorrhea are routinely treated for both pathogens.

Urethritis in men – anterior urethritis is the most common manifestation in men and presents with a purulent urethral discharge and/or dysuria. The discharge may be profuse, minimal or undetectable. Erythema of the urethral meatus may occur. The initial infection is asymptomatic in 5% of men. Complications include prostatitis, epididymitis (presents with unilateral testicular pain and swelling), urethral stricture, and disseminated gonococcal infection (see below).

Urogenital infection in women – the endocervical canal is the primary site of infection (mucopurulent cervicitis). The urethra may be involved as well (urethritis). Symptoms include vaginal discharge, pelvic pain, dysuria, frequent urination, and abnormal uterine bleeding. **The majority of infected women are asymptomatic, and many present for treatment only after referral from a symptomatic male partner.** Untreated infection can result in pelvic inflammatory disease and infertility (see below). Other complications include Bartholin's glands abscess or infection (manifest as labial pain and swelling) and perihepatitis (**Fitz-Hugh-Curtis** syndrome which involves right upper quadrant abdominal pain and tenderness and elevated liver enzymes; due to direct extension of gonorrhea or chlamydia from the fallopian tube to the liver capsule and overlying peritoneum).

Rectal infection/proctitis can occur in both men and women. In men rectal gonorrhea is common among men who have sex with men. In women, rectal infection can occur from contamination of the rectum by infected vaginal secretions or by rectal intercourse. Symptoms include anal irritation, painful defecation, bleeding, cramping, constipation and mucopurulent rectal discharge. Many patients with rectal infection are asymptomatic.

Pharyngeal infection results from orogenital contact and is usually asymptomatic, but can cause exudative pharyngitis and cervical adenitis, and can be a source of further transmission.

Pelvic inflammatory disease (PID) refers to infection of the endometrium (endometritis), fallopian tubes (salpingitis) and/or surrounding peritoneum (pelvic peritonitis) which occurs as a complication of cervicitis, due to ascending infection. 10-20% of women with gonorrhea develop PID. Often, more than one organism is isolated (chlamydia, anaerobes). Signs and symptoms include lower abdominal pain, fever, dyspareunia (pain during intercourse) and vaginal bleeding. Signs include mucopurulent endocervical discharge, cervical motion tenderness (pain during

movement of the cervix during pelvic exam), uterine or adnexal tenderness, fever, an elevated white blood cell count, and an elevated erythrocyte sedimentation rate (ESR) or C-reactive protein. Tubo-ovarian abscesses can also occur. Tubal scarring can lead to infertility (the most common serious consequence of PID) and ectopic pregnancy. Infertility has been identified in approximately 1 in 5 women after one episode of PID, and the risk rises with subsequent PID episodes. The incidence of ectopic pregnancy increases 7-fold with 1 episode of PID. The clinical diagnosis of PID (vs. laparoscopic findings) is imprecise -- insensitive and nonspecific.

Disseminated gonococcal infection – DGI results from gonococcal bacteremia and occurs in 1-3% of infected patients. Symptoms include fever, skin lesions (pustules, sometimes hemorrhagic or necrotic, on an erythematous base, located mostly on the extremities), tenosynovitis (inflammation of a tendon and its enveloping sheath), oligoarthritis (inflammation of a few joints, most commonly knee, also elbows, ankles, wrists, small joints of hands and feet), and migratory polyarthralgias (joint pain). This presentation is called the arthritis-dermatitis syndrome. Untreated, overt septic arthritis in one or two joints may occur. Rarely, hepatitis, endocarditis, or meningitis can occur. Deficiency in the terminal complement components (C5-8) may increase susceptibility to disseminated infection. Female sex and menstruation are associated with disseminated infection.

Perinatal disease – the neonate may develop gonococcal conjunctivitis **(ophthalmia neonatorum)** due to passage through an infected birth canal. It presents as a severe sight-threatening bilateral conjunctival inflammation. Administration at birth to all neonates of 1% silver nitrate, 1% tetracycline, or 0.5% erythromycin eye ointments protects against the development of ophthalmia neonatorum.

Diagnosis

A **Gram stain** of urethral discharge showing intracellular Gram negative diplococci is >90% sensitive and >98% specific in symptomatic men for the diagnosis of gonococcal urethritis. The Gram stain is less reliable in women and asymptomatic men. In these cases diagnosis is confirmed by culture or nucleic acid amplification of affected sites.

Cultures of urethral, cervical, rectal, and pharyngeal specimens must be inoculated onto selective media (e.g., modified Thayer-Martin medium) to suppress the growth of contaminating organisms. For best sensitivity, inoculation should also occur onto nonselective media (e.g., chocolate blood agar) because some gonococcal strains are inhibited by the vancomycin present in most selective media.

Nucleic acid amplification assays for *N. gonorrhoeae* (including polymerase chain reaction, transcription-mediated amplification, and strand displacement amplification) have been developed for use with clinical specimens (urine, urethral, cervical). These assays are highly sensitive and specific, and in many laboratories these assays have replaced culture. Combination assays for both *N. gonorrhoeae* and *Chlamydia* organisms are available.

Treatment

Third generation cephalosporins (a single intramuscular injection of ceftriaxone or a single oral dose of cefixime) are the treatment of choice for uncomplicated gonococcal urethritis or cervicitis. Penicillin was used in the past, but plasmid-mediated B-lactamase production and chromosomally mediated changes in penicillin-binding proteins and in cell wall permeability have rendered penicillin much less useful. Until very recently, quinolones were also used but the increasing incidence of infection with quinolone-resistant gonococcal strains led the CDC, in 2007, to recommend that quinolones no longer be used for the treatment of gonococcal infections.

Coinfection with C. trachomatis often occurs, so presumptive treatment for chlamydia (with

either a single dose of azithromycin or a 1-week course of doxycycline) is appropriate. Recent sex partners (within 60 days of onset of symptoms) should be referred for evaluation and treatment for *N. gonorrhoeae* and *C. trachomatis*. Treatment of pelvic inflammatory disease is more complicated and prolonged, and should include coverage of *N. gonorrhoeae*, *C. trachomatis*, anaerobes, Gram negative rods, and streptococci.

Prevention involves education regarding safer sex practices, aggressive detection, rigorous follow-up screening and treatment of sexual contacts, and screening of asymptomatic at-risk persons. No vaccine is available to prevent gonorrhea.

_____ Chlamydia _____

Chlamydia trachomatis causes asymptomatic infection as well as urethritis, cervicitis, pelvic inflammatory disease, and (certain serovars) lymphogranuloma venereum. Note: *Chlamydophila pnemoniae* and *Chlamydophila psittaci*, also in the family chlamydiaceae, cause respiratory illnesses discussed elsewhere.

Epidemiology
C. trachomatis is thought to be the most common sexually transmitted bacterial disease in the U.S. It is estimated that 3 million Americans are infected each year, **the majority of whom are asymptomatic**. The prevalence of chlamydial infection ranges from 3-5% of asymptomatic men and women seen in general medical clinics, to 15-20% of those seen in STD clinics. It is most prevalent in sexually active adolescents.

Microbiology and Pathogenesis
Chlamydiae are obligate intracellular parasites that have inner and outer membranes similar to those of Gram negative bacteria, but they lack the rigid peptidoglycan layer found in most other bacteria. They replicate within host cells via a unique growth cycle involving two morphological components -- the stable elementary body, which can persist in the extracellular environment and is responsible for host-host and cell-cell transmission, and the reticulate body, which replicates inside the cell and cannot survive outside. The cycle is initiated when the small, infectious elementary body attaches to the host epithelial cell and enters the cell by endocytosis within a vacuole that is derived from the host cell membrane. In this cytoplasmic phagosome, phagolysosomal fusion is inhibited. About 8 hours after entering a host cell, the initially metabolically inactive elementary body becomes the metabolically active reticulate body which uses the host cell ATP for its energy requirements. The reticulate bodies replicate by binary fission, and can be detected by histologic stains (the phagosome with accumulated reticulate bodies is called an **inclusion**). The reticulate bodies then reorganize into the smaller elementary bodies, and about 48-72 hours after infection the cell ruptures and releases infectious elementary bodies.

The clinical features of chlamydial infections are caused by the direct destruction of cells during replication as well as the host inflammatory response (infection causes secretion of TNF and IL-6 and infiltration of neutrophils). Chlamydiae have been found to possess a type III secretion apparatus comparable to that found in other Gram negative bacteria, which probably serves as a means of transporting chlamydial proteins outside the inclusion membrane, where they may regulate host cell transcription, perhaps facilitating key events such as inhibition of fusion of the chlamydial inclusion with host cell lysosomes. Infection does not confer long-lasting immunity. Instead, reinfection is frequent and often induces a vigorous inflammatory response with subsequent tissue damage.

Clinical Features
Specific serovars (serologic variants which are categorized on the basis of antigenic differences in the major outer membrane protein) are associated with specific disease. Lymphogranuloma venereum (LGV) is associated with serovars L1 to L3 and is discussed below. Endemic trachoma (chronic keratoconjunctivitis that is endemic in the Middle East, North Africa, and India and is a cause of blindness) is associated with serovars A to C and is not discussed further. Most genital tract infections (except LGV) are caused by serotypes D through K.

Urethritis in men – The incubation period is 7-21 days. Symptoms include dysuria, urethral discharge, and urethral itching. Nongonococcal urethritis (NGU) is a diagnosis applied to men with symptoms or signs of urethritis who do not have gonorrhea. Postgonococcal urethritis (PGU) refers to nongonococcal urethritis which develops 2 weeks after treatment of gonococcal urethritis in men. *Chlamydia trachomatis* causes 50% of NGU and PGU, other etiologies including *Ureaplasma urealyticum, Mycoplasma genitalium, Herpes simplex,* and *Trichomonas vaginalis*. (If a patient is co-infected with gonorrhea and chlamydia, symptoms of the chlamydial infection may develop after successful treatment of the gonorrhea, because the incubation period is longer and the use of B-lactam antibiotics to treat gonorrhea would be ineffective against *C. trachomatis*.) Patients with urethritis frequently have pyuria (white blood cells in urine, particularly first-catch urine) and increased leukocytes on Gram stain of a urogenital swab ($\geq$5 WBCs per oil immersion field). *C. trachomatis* urethritis is generally less severe than gonococcal urethritis, but the two cannot reliably be distinguished on clinical grounds alone. One must test, and frequently treat, for both. A substantial proportion of men (as many as 25%) with *C. trachomatis* urethritis are asymptomatic. An estimated 5-10% of male STD patients have asymptomatic *C. trachomatis* urethral infection. Complications and other infections in men include epididymitis, prostatitis, proctitis, and Reiter's syndrome (this triad of arthritis, conjunctivitis, and urethritis +/- skin lesions is thought to be due to chlamydia in 70% of cases).

Cervicitis and PID – The majority of women with cervicitis due to *C. trachomatis* (as many as 80%) are asymptomatic and have a normal cervical examination, but mucopurulent cervicitis can be seen. Symptoms include pelvic pain, vaginal discharge, abnormal vaginal bleeding, and dysuria. Complications include **Bartholinitis** (infection of Bartholin's ducts), and **pelvic inflammatory disease (PID),** as discussed in the gonorrhea section. Pelvic inflammatory disease due to chlamydia and gonorrhea is an enormous public health problem leading to infertility and ectopic pregnancy. Control of PID is complicated by the high frequency of asymptomatic cervical infections.

Urethritis in women – *C. trachomatis* is one of the etiologic agents in the acute urethral syndrome and a cause of sterile pyuria (WBCs in the urine, but negative urine culture). The symptoms of dysuria and urinary frequency can be misdiagnosed as bacterial urinary tract infection. Urethral discharge may be seen and Gram stain of urethral discharge may reveal increased polymorphonuclear leukocytes. Urethritis may occur in the presence or absence of cervicitis.

Proctitis can occur in both men and women through anal intercourse or, in women, due to spread of secretions from the cervix. Symptoms include anal pruritus and mucopurulent rectal discharge.

Perinatal infection – Neonatal conjunctivitis involving a copious purulent discharge can develop in infants exposed to *C. trachomatis* at birth (**newborn inclusion conjunctivitis**). This is not prevented with the administration at birth of antimicrobial drops, and is treated with oral

erythromycin (a macrolide). The possibility of concomitant chlamydial pneumonia should be considered. NOTE: Inclusion conjunctivitis can also occur in adults, often due to autoinoculation with infected genital secretions.

Lymphogranuloma Venereum (LGV) – Caused by serovars L1, L2, and L3, LGV is endemic in areas of Africa, SE Asia, India, South America and the Caribbean. It occurs sporadically elsewhere. However, recently there has been an ongoing outbreak of LGV proctitis among men who have sex with men in Europe, Canada, and the U.S. After an incubation period of 3-30 days, a primary lesion (papule or ulcer, usually painless) appears at the site of infection. Days to weeks later, the secondary stage occurs, involving constitutional symptoms such as fever, headache, and myalgias, and inflammation of the lymph nodes draining the site of infection. The inguinal nodes, most commonly involved, can become painful, fluctuant **buboes** that can enlarge and rupture, forming draining fistulas. Untreated LGV may progress to a chronic ulcerative phase involving lymphatic obstruction, genital elephantiasis, urethral or rectal strictures, and chronic hard inguinal masses. LGV proctitis can be misdiagnosed as Crohn's disease.

Diagnosis

Diagnostic tests should also include tests for *N. gonorrhoeae*.

Nucleic acid amplification tests (including polymerase chain reaction, transcription-mediated amplification, and strand displacement amplification) are currently considered the tests of choice for the laboratory diagnosis of genital *C. trachomatis* infection. They are highly sensitive and specific (90-98%) and can be performed on urethral and cervical samples as well as urine and vaginal swabs. Combination assays for both *N. gonorrhoeae* and *Chlamydia* organisms are available.

C. trachomatis may be isolated in **cell culture** from urethral and cervical specimens but requires adequate sampling, quick transport, and special cell lines. Culture is not as sensitive as nucleic acid amplification tests and is not routinely used for the diagnosis of genital chlamydial infections.

Serology is of limited value in the diagnosis of genital infections in adults because antibody titers can persist for a prolonged period of time, and adults often do not produce IgM antibodies. Thus distinction between current and past infections is not possible. However, serologic testing is useful in the diagnosis of LGV.

Treatment

Uncomplicated urethritis or cervicitis should be treated with one dose of azithromycin (a macrolide) or a 7-day course of doxycycline (a tetracycline). LGV should be treated with doxycycline for 21 days. All sex partners within the preceding 60 days should be evaluated and treated.

Prevention involves education regarding safer sex practices, prompt treatment of symptomatic patients and their sexual partners, and screening and treatment of at-risk asymptomatic patients. The United States Preventive Services Task Force (USPSTF) and the Centers for Disease Control (CDC) recommend screening for *Chlamydia trachomatis* at the time of the annual pelvic examination for all sexually active women age 25 years or younger, and sexually active women older than 25 years with risk factors (e.g., more than one sex partner, a new sex partner). Sexually active men who have sex with men should be screened for chlamydia and gonorrhea at least annually. The sensitivity of the nucleic acid amplification tests performed on urine is nearly identical to the sensitivity with more invasive specimens such as urethral swabs and cervical specimens, and availability of this non-invasive screening technique (as well as, possibly, self-

collected vaginal swabs) has been shown to improve adherence to screening guidelines. No vaccine is currently available.

Herpes

Herpes simplex virus causes ulcerative genital disease, a recurrent, life-long viral infection. The microbiology and pathogenesis of herpesviruses will be discussed at further length in Dr. Gershon's lectures. For the purposes of this lecture, Herpes simplex virus types 1 and 2 are DNA viruses that tend to produce latent and recurrent infections. That is, after primary infection, the virus remains latent in the dorsal root ganglia for the lifetime of the patient, and can periodically reactivate, causing viral shedding, risk of transmission, and risk of recurrence of symptoms.

Epidemiology
At least 50 million persons in the U.S. have genital HSV infection. Genital herpes infections are primarily caused by HSV-2. However, HSV-1, which more frequently causes orolabial lesions (gingivostomatitis) and keratitis, can also cause genital lesions, but recurrent HSV-1 genital lesions are much less frequent. **Most persons infected with HSV-2 have not been diagnosed**. Many such persons have mild or unrecognized infections but shed virus intermittently in the genital tract, and transmission to others can occur during asymptomatic viral shedding. **Most genital herpes infections are transmitted by persons unaware that they have the infection or who are asymptomatic when transmission occurs.** Approximately 60% of men and women infected with HSV-2 may not have symptomatic outbreaks and may be unaware of their infection. Herpes simplex and all other genital ulcer diseases have been associated with increased transmission of HIV, and it is postulated that better control of herpes may help in the worldwide battle against HIV. Clinical trials are underway to determine whether suppressive treatment of HSV decreases transmission of HIV.

Pathogenesis
(This will be discussed more fully during Dr. Gershon's lectures.) Primary infection with HSV occurs through mucosal membranes or breaks in the skin. The virus replicates locally in mucoepithelial cells, causing disease at the site of infection, and then moves along sensory nerves to the ganglia where it becomes latent. Reactivation occurs with spread of virus peripherally along sensory nerves to the skin sites, where a new lesion develops with inflammatory response.

Clinical Features
During primary genital HSV infection, many patients have systemic symptoms including fever, malaise, headache. Local symptoms include pain, itching, dysuria, and vaginal or urethral discharge. Tender inguinal lymphadenopathy develops. Herpes infections are characteristically painful fluid-filled vesicles that evolve into pustules and finally to shallow ulcers on an erythematous base. Multiple lesions are common, and they may erupt in tightly grouped clusters. Lesions can coalesce into large painful ulcers. In women, primary HSV infection is associated with recovery of virus from the cervix in approximately 80% of cases. The lesions range from a severe erosive cervicitis to mild erythema and small herpetic lesions. The duration of the primary disease usually averages about 21 days. Five to ten percent of patients will actually have aseptic meningitis manifested by nuchal rigidity, headache, photophobia, and a CSF lymphocytic pleocytosis.

Recurrences of genital herpes after primary infection have been recorded in over 70% of patients followed over a period of 9 months. The clinical manifestations of recurrent disease are markedly different from those of primary disease, being milder in symptom and shorter in duration.

Recurrent lesions are usually smaller in number and usually unilateral, and about 50% of patients experience prodromal symptoms consisting of tingling or pain at the site of eruption which occur 24-48 hours prior to the appearance of lesions.

Complications include aseptic meningitis, transverse myelitis, and perinatal transmission. Herpes simplex virus infection of the newborn is acquired through contact of the infant with active virus as a result of its passage through the infected birth canal. As a consequence of the immaturity of the infant's immune system, the acquisition of neonatal herpes is often associated with dissemination of the disease, and organ involvement, e.g., of spleen, liver, lung and heart, along with severe neurological damage, may occur. Disease localized to the skin or eye has also been reported. The risk of neonatal HSV infection is greatest in a woman who develops primary genital herpes near term. Most specialists recommend that women with active genital HSV lesions at the onset of labor deliver by caesarean section to protect the baby from infection.

Diagnosis

Diagnosis of HSV can be confirmed via **viral culture,** or detection of antigen with **direct fluorescent antibody**. Detection of DNA (using in situ hybridization or PCR) is becoming increasingly available. Sensitivity of culture is maximized if the base of the ulcer is scraped and if the test is performed earlier in the course, before healing begins. Cytologic detection of cellular changes of herpes virus infection (Tzanck preparation, looking for characteristic multinucleated giant cells and intranuclear inclusions) is neither sensitive nor specific in genital lesions and should not be relied on for diagnosis of genital herpes infection. **Serologic tests** that differentiate between HSV-2 and HSV-1 (based on glycoprotein G) can be helpful in certain circumstances. These antibodies develop during the first several weeks following infection and persist indefinitely, and so are not typically used to establish the role of HSV as a cause of an acute genital lesion. However, they can be used to diagnose persons with unrecognized infection and to manage sex partners of persons with genital herpes. Presence of HSV-2 antibody indicates anogenital infection, but presence of HSV-1 antibody cannot distinguish between anogenital and orolabial infection.

Treatment

Treatment with oral acyclovir, famciclovir, or valacyclovir during primary infection can decrease the duration and severity of symptoms but it will not prevent recurrence of disease. During recurrent disease, treatment with the same oral medications at lower doses and for shorter duration can be used at the onset of symptoms to decrease the time to healing and the duration of viral shedding. Use of daily suppressive therapy can be used to reduce recurrences (by as much as 80%) and may be beneficial to patients with severe or frequent recurrences. Suppressive antiviral therapy reduces but does not eliminate subclinical viral shedding. Daily suppressive therapy with valacyclovir has been shown in a clinical trial to reduce transmission of genital herpes infection among monogamous, heterosexual, HSV-2 serodiscordant couples by approximately 50%. Symptomatic sex partners should be evaluated and treated. Asymptomatic sex partners should be offered type-specific serologic testing to determine whether risk for HSV acquisition exists.

Prevention

Condoms can reduce the risk for genital herpes if the infected areas are consistently and correctly covered by the condom. As above, suppressive treatment has been shown to decrease transmission. HSV vaccines are currently being tested in clinical trials.

Syphilis

Syphilis, the cause of a substantial proportion of genital ulcers, and a leading agent in the differential diagnosis of HSV, was discussed in a previous lecture. Classically, the HSV ulcer is painful while the syphilitic chancre is painless. However, the two are difficult to differentiate, and microbiologic testing to confirm a diagnosis is required. Evaluation of all patients with genital ulcers should include at least a serologic test for syphilis and a diagnostic evaluation for genital herpes, as well as microbiologic tests for other causes of genital ulcer diseases as appropriate. More than one of these diseases may be present in a patient who has genital ulcers. As with other STDs, any patient with genital ulcers should be offered HIV testing, as all diseases characterized by genital ulcers have been associated with an increased risk for HIV infection.

Other genital ulcer diseases

Chancroid is caused by the bacterium *Haemophilus ducreyi*. It is relatively uncommon in the U.S. but increasingly common in New York and is frequently encountered in Africa. Most cases occur in men. Chancroid is a major risk factor for increased transmission of HIV because of the ulcerations. After an incubation period of 2-5 days a small macule develops then ulcerates. The resulting ulcer, which can occur on the penis or anus in men and the vulva or vagina in women, is markedly painful, with ragged undermined edges and a base which may be covered with a gray or yellow exudate. Expansive, tender lymph nodes called **buboes** can occur and often become fluctuant, sometimes with spontaneous drainage. Satellite lesions may develop, but a solitary lesion is most common. Diagnosis is made by culture of the organism or by seeing the organisms on aspiration of a lesion (Gram negative slender rods or coccobacilli). *H. ducreyi* is difficult to grow, requiring specialized media. A PCR-based assay has been developed but is not yet commercially available. Therapy is with a single dose of azithromycin (a macrolide), a single injection of ceftriaxone (a 3rd-generation cephalosporin), or a 3-day course of ciprofloxacin (a quinolone). Sex partners should be examined and treated, regardless of whether symptoms of the disease are present, if they had sexual contact with the patient during the 10 days preceding the patient's onset of symptoms.

Granuloma Inguinale (Donovanosis) is a genital ulcerative disease caused by *Calymmatobacterium granulomatis*, a Gram negative bacillus. It is uncommon in the U.S. but endemic in Papua New Guinea and parts of India, southern Africa, the Caribbean, and South America. Disease begins as a small, **painless** subcutaneous nodule in the genital area which then ulcerates **without** regional lymphadenopathy. The diagnosis is made by the demonstration with Wright's or Giemsa's stain of dark-staining Donovan bodies in a smear of the lesion or histologic study of the tissue involved. Treatment is with doxycycline, azithromycin, ciprofloxacin, or trimethoprim-sulfamethoxazole for at least 3 weeks.

Lymphogranuloma venereum (LGV) was previously discussed because it is caused by *Chlamydia trachomatis*, but should be included in the list of causes of genital ulcers.

Human papillomaviruses (HPV)

Human papillomaviruses (HPV) are double-stranded DNA viruses that cause anogenital warts (condylomata acuminata [plural], condyloma acuminatum [singular]) and are associated with anogenital malignancy including cervical, vaginal, vulvar, penile, and anal carcinoma. HPV is the most common viral STD in the U.S.

Epidemiology
The true prevalence of HPV infection is unknown because most infections are subclinical and HPV is not a reportable disease, but it is believed to be very common, especially among young sexually active women. It is estimated that 6.2 million new infections occur each year in the U.S. It is spread by unprotected penetrative intercourse and close physical contact involving an infected area. Risk of HPV in women is related to the number of male sex partners and to the male partners' number of female sex partners. A study of female college students revealed 26% to be HPV-positive (by HPV DNA detection in cervicovaginal lavage) at baseline, and 43% of the initially HPV-negative women acquired HPV during three-year follow-up. Fortunately, the infections are usually transient (clear within 2 years), and the prevalence of cervical HPV infection falls quickly after age 30. Women with persistent infection are at highest risk for the development of high-grade cervical intraepithelial neoplasia (CIN) and cervical cancer. The prevalence of HPV in heterosexual men is unknown, although presumably substantial, **and it is felt that men and women with asymptomatic infection fuel transmission of this virus**. Men who have sex with men have a prevalence of anal HPV infection as high as 57%. Widespread screening for and treatment of cervical dysplasia with Pap smears has markedly decreased the incidence of cervical cancer in the developed world, but worldwide cervical cancer remains the second most common cancer in women.

Microbiology and Pathogenesis
There are more than 100 types of HPV, and more than 25 of these have been isolated from the genital tract. Benign anogenital warts are most frequently caused by HPV types 6 and 11, which are "low risk" for the development of neoplasia. HPV types 16 and 18 are associated with intraepithelial neoplasia of the cervix, vulva, penis, and anus, and have been unequivocally linked to cervical cancer (at least 15 types of HPV, including 31, 33, and 35, have been categorized as high-risk for the development of intraepithelial neoplasia, but the majority of cervical cancers are linked to HPV types 16 and 18.) An individual can be infected with more than one type. Note: several types of cutaneous HPV (types 1 and 2, for example) cause non-genital cutaneous warts.

Persistent infection with an oncogenic HPV increases the risk of high-grade intraepithelial neoplasia and cervical cancer, while transient infection (most HPV infections) poses substantially less risk. HPV infects the epithelium, and can either persist in the nucleus extrachromosomally or integrate into the host genome. Viral integration results in overexpression of the oncoproteins E6 and E7 which leads to disabling of two major tumor suppressor gene products, the p53 tumor suppressor gene product and the retinoblastoma protein, which is thought to enable host cell immortalization. (HPV will be discussed in greater detail during the oncology section.)

Clinical features
Anogenital warts (condylomata acuminata) can occur on the penis, vulva, vagina, cervix, perineum, and anus. Lesions are flesh- to gray-colored, single or multiple papules which vary in size from less than a millimeter in diameter to several centimeters (if lesions coalesce), and can be flat, relatively inconspicuous papules or verrucous, pedunculated, or cauliflower-like masses. They may be associated with burning and itching but are usually asymptomatic. Women with external genital lesions often have cervical or vaginal involvement. The incubation period is usually 4-8 weeks, but the wart may not become apparent for up to 6 months. Condylomata acuminata need to be distinguished from condylomata lata of secondary syphilis.

Anogenital squamous intraepithelial neoplasia: As noted above, a strong association exists between persistence of high-risk HPV types and squamous intraepithelial neoplasia (SIN) of the cervix (cervical intraepithelial neoplasia, or CIN), anus, vagina, vulva, and penis. Left untreated, such infection can progress to squamous cell carcinoma of the affected site. Cervical HPV

infection is the primary cause worldwide of cervical cancer. Note: HPV has also been linked to some cancers of the oropharynx.

Diagnosis: There is no cell culture system for the cultivation of HPV. The presence of virus in nonkeratinized tissues (e.g., cervix) can be assessed by cytologic methods (PAP smear) or biopsy. The cytologic change consistent with HPV is the koilocyte (large squamous cell with a clear halo around a shrunken nucleus) with or without nuclear atypia. Diagnosis involves careful external genitalia exam and, in women, a speculum exam involving a Pap smear for the detection of cervical atypia, and, when appropriate, the application of acetic acid to the cervix to help identify, with the aid of colposcopy, suspicious lesions for biopsy (one need not biopsy typical-appearing genital warts – biopsy is for areas of concern for dysplasia). Some experts recommend cytologic screening for anal HPV infection in men or women who engage in receptive anal intercourse. Detection of HPV DNA by molecular-based assays, for example in situ hybridization and PCR, is a newer, potentially very valuable technique, but its exact role in the management of HPV infection is not yet determined. (For example, though, perhaps eventually women with abnormal Pap smears in whom no high-risk HPV type is identified might be spared frequent colposcopy and cervical biopsies.) The details of cervical and anal cytologic screening and follow-up are beyond the scope of this lecture.

Treatment of genital warts can be based on physical disruption (cautery, excision, freezing, laser), chemical disruption (podophyllotoxin, trichloroacetic acid), or immunomodulation (imiquimod). Treatment may be applied topically or intralesionally.

Prevention

Consistent use of condoms may decrease the transmission of HPV infection, but transmission can occur without intercourse, e.g. from scrotum to vulva during foreplay. However, randomized studies have shown that male condom use promotes regression of CIN and clearance of HPV DNA in the female sexual partners as well as regression of HPV-associated penile lesions in the male partner. In a recent longitudinal cohort study among newly sexually active women, consistent condom use by their partners appeared to reduce the risk of cervical and vulvovaginal HPV infection (NEJM 2006:354:2645-54). Once a woman has become infected with HPV, regular Pap smears and follow-up/treatment of abnormal smears is highly effective at preventing the development of cervical cancer. Investigation is under way to determine if screening anal Pap smears in men who engage in anal intercourse will prevent the development of anal carcinoma. In the summer of 2006, a vaccine which targets HPV types 6, 11, 16, and 18 (the types primarily responsible for genital warts and cervical cancer) was approved by the FDA for use in girls/women ages 9 to 26 years. In young women who had not previously been exposed to any of the four vaccine HPV types, the vaccine was shown to be 100% effective in preventing cervical dysplasia caused by the vaccine HPV types. The Advisory Committee on Immunization Practices (ACIP) recommended in June 2006 that the vaccine be routinely given to girls when they are 11-12 years old. The ACIP recommendation also allows for vaccination of girls beginning at 9 years old as well as vaccination of girls and women 13-26 years old. Routine Pap smear screening will continue to be necessary, as the vaccine does not protect against all types of HPV.

Vaginitis

Vaginitis is briefly included here because some causes of vaginitis may indeed be sexually transmitted, and because the symptoms of vaginitis overlap with those of cervicitis. Like cervicitis, vaginitis/vaginosis results in vaginal discharge. Vaginitis may present as an increase in the amount, odor, or color of vaginal discharge, as well as itching, dysuria, dyspareunia, or vulvar irritation. The three most common causes of vaginal discharge are bacterial vaginosis (BV, 40-50% cases), vulvovaginal candidiasis (20-25%), and trichomoniasis (15-20%). Both BV and trichomoniasis may be associated with increased risk of acquisition of HIV infection. Diagnosis relies on speculum examination and microscopic examination of the vaginal discharge. Vaginitis can be treated with topical or oral therapy, and the specific agent depends on the type of vaginitis.

Bacterial vaginosis (BV) is a clinical syndrome resulting from a shift of the normal vaginal flora from predominantly lactobacilli to increased numbers of *Gardnerella vaginalis, Mobiluncus* species, and other anaerobes. BV is probably not sexually transmitted, although sexual activity may increase the risk of BV through changes in vaginal pH, and BV is associated with having multiple sex partners. Routine treatment of sexual partners of women with BV is not recommended. Diagnosis is aided by the visualization on microscopic examination of clue cells (vaginal squamous epithelial cells covered with bacteria), pH of vaginal fluid > 4.5, and a fishy odor of the discharge before or after addition of 10% KOH (the whiff test).

Vulgovaginal candidiasis (due to excessive growth of the fungus *Candida* (usually *Candida albicans*) often occurs in the setting of recent antibiotics, HIV, poorly controlled diabetes mellitus, and pregnancy; but it occurs overall most frequently in women without such risk factors. Vulgovaginal candidiasis is not usually acquired sexually, and treatment of sex partners is not recommended, but may be considered in women with recurrent infection. Use of 10% KOH in microscopic evaluation of vaginal discharge improves the visualization of the yeast. Vaginal culture can also confirm the diagnosis.

Trichomonal vaginitis is caused by the protozoan, *Trichomonas vaginalis*. Male partners of women with trichomonal vaginitis are frequently infected, so treatment of sexual partners is routinely recommended. Tiny hemorrhages may be seen on the cervix ("strawberry cervix"). Diagnosis may be confirmed by visualizing mobile trichomonads on microscopic examination of the vaginal discharge, but culture is more sensitive.

The CDC's treatment guidelines for STDs is a good reference for up-to-date treatment recommendations.

> Centers for Disease Control and Prevention. **Sexually Transmitted Diseases Treatment Guidelines 2006**. MMWR 2006;55(No. RR-11) (available at http://www.cdc.gov/std/treatment/default.htm) and the **Update to CDC's Sexually Transmitted Diseases Treatment Guidelines, 2006: Fluoroquinolones No Longer Recommended for Treatment of Gonococcal Infection.** MMWR April 13, 2007;56(14)332-336.
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