Sexually Transmitted Agents

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Global Incidence Rates of STDs: 330 Million New Infections Yearly

HPV	200+ million/yr?
Trichomonas	170 million/yr
Chlamydia	89 million/yr
Gonorrhea	62 million/yr
Genital Warts	30 million/yr
Herpes	20 million/yr
Syphilis	12 million/yr
HIV	5.5 million/yr
Hepatitis B	2.5 million/yr
Chancroid	2 million/yr

Global Impact of STDs

STDs are a large cause of morbidity and mortality across the world. Complications include congenital infection, infertility, ectopic pregnancy, cancers, enhanced transmission of HIV.

HIV and the Other STDs

Prospective epidemiologic studies on 4 continents have repeatedly demonstrated that when other STDs are present, HIV transmission is 2-5 times higher

Inflammatory STDs: 2-5
Ulcerative STDs: 5-9

Additionally, the presence of HIV infection increases an individual's susceptibility to infection with the other STDs. Thus, if the other STDS are better controlled, HIV transmission will decrease, and vice versa.

National Incidence Rates of STDs

Of the top ten reportable diseases, 5 were STDs. There are 20 million new STD infections in the US annually, and nearly half of these will occur in adolescents/young adults (15-24).

Top 10 Notifiable Diseases in the U.S., 2010:

1. Chamydia	1,210,523
2. Gonorrhea	336,742
3. Salmonellosis	51,040
4. Syphillis	46,277
5. AIDS	39,202

6. Lyme disease	35,918
7. Varicella	30,386
8. Shigellosis	22,625
9. Giardiasis	18,908
10. Pertussis	13,278

Why haven't STDs disappeared in the U.S.?
We have national screening recommendations, improved diagnostic techniques, and highly-effective single dose therapies for many of the diseases. Reasons are multifactorial and include The fact that people still have unprotected sex! Treatment is not always adequate because clinicians do not keep up with the most recent treatment guidelines, and thus treat with ineffective antibiotics. Further, the asymptomatic nature of many of these infections allow for them to go unsuspected, undiagnosed, and thus continuing the cycle of transmission. Additionally there are gender differences and specific subpopulations at increased risk (e.g. adolescents and men who have sex with men (MSM))

Gender Differences in STDs
Women are biologically more susceptible, often asymptomatic or minimally so, more difficult to diagnose, and more likely to suffer more frequent and more serious health complications.

Adolescents and STDs
Adolescent females do not have full cervical maturity that can lead to enhanced risk of infection with gonorrhea and chlamydia. One in four teens have an STD in the US. Adolescents can be a challenging subpopulation with respect to having access to healthcare services. Often STDs are not discussed during routine visits to physicians.

Prevention & Control of Bacterial STDs
Regardless of which STD is involved, prevention and control will include some combination of partner tracing, identification, and notification along with epidemiologic treatment of partners. This means that all identified partners of a patient with a bacterial STD will be offered prophylactic therapy for that STD regardless of symptoms. Enhanced educational initiatives among the subpopulations most at risk are critical to controlling and decreasing incidence rates. One example was the decrease in HIV and other STDS among MSM populations in the late 1980's through the 1990s. Education around consistent and correct use of condoms is important. Vaccines are still not available for the bacterial STDS, though not for lack of trying. Thus far, microbicides have not been shown to be an effective mechanism for bacterial STD prevention.

Gonorrhea and Chlamydia: General Information
They are the 2 most common bacterial STDs. The 2 organisms are bacteriologically very different, however they cause clinically indistinguishable syndromes. They cause the inflammatory STDS. The clinical syndromes caused by gonorrhea and chlamydia are as follows. In men they cause urethritis and epididymitis. In women they cause mucopurulent cervicitis, Pelvic inflammatory disease (PID), tubo-ovarian abscess (TOA), peritonitis, the dysuria-pyuria syndrome, and the rare complication known as Fitzhugh-Curtis syndrome (This is an inflammation of Glisson's capsule of the liver). Both men & women can have the following

manifestations of gonorrhea and chlamydia infection: conjunctivitis and anorectal infection. Only gonorrhea can cause a pharyngitis. Only chlamydia can cause neonatal pneumonia. Sequelae can include disseminated gonococcal infection (DGI) in patients with gonorrhea, and reactive arthritis (formerly known as Reiter's syndrome) for both.

Gonorrhea: Physiology and Structure

Neisseria gonorrhoeae ("flow of seed") is a Gram negative diplococcus with typical Gram negative structure including an outer membrane, peptidoglycan layer, and inner membrane. It has no capsule. It is very fastidious and requires special media and 5% CO_2 for isolation in culture.

Gonorrhea Physiology and Structure: Virulence Factors

The organism has pili that allow for attachment to host cells. Additionally the antigenic variation of the pili allows for no significant immunity to develop, and re-infection to occur.
The Por Protein is another virulence factor that promotes intracellular survival of the organism by allowing it to evade destruction by the phagolysosome. The Opa Protein: mediates binding to epithelial cells. The organism also has a Lipooligosaccharide in its cell membrane, and β lactamase enzymes, which promote penicillin resistance.

Gonorrhea: Pathogenesis and Immunity

The organism attaches to mucosal cells via pili and penetrate into the cells. It then establishes infection in the subepithelial space. The lipooligosaccharide stimulates an inflammatory response that includes release of TNF and other cytokines, WBCs are called in, and this response results in the inflammatory response and clinical findings of an "itis" and discharge.

Gonorrhea: Epidemiology

Humans are the only natural host. The route of transmission is direct mucosal contact with infected mucous membranes or fluids. The organism does not survive well outside the body: no transmission on toilet seats! The epidemic exists in adolescents where case rates 6-7 times higher than the general population.

Gonorrhea Epidemiology: Symptomatic or Not?

90% of males infected with *N. gonorrhoeae* become symptomatic within 5-7 days of infection. At most, 50% of women become symptomatic within 2 weeks of infection. **Screening is essential!**

Gonorrhea: Laboratory Diagnosis

The diagnosis can be made in men with urethritis when a Gram stain of the urethral discharge reveals the intracellular Gram negative diplococci. Culture was the most common way to make the diagnosis until the 1990s. The organism is fastidious and requires selective media in order to grow in the lab. One preferred media is modified Thayer-Martin media. Always culture all potentially exposed sites in order to increase the ability to make a definitive diagnosis, when culture-bases diagnostics are being used. Non-culture based diagnostics have become the gold standard over the last 2 decades. There are several advantages to these tests including that they do not require media or CO2 atmosphere for viability. These tests are PCR and other Nucleic acid amplification tests (NAATs). There are now combination assays for gonorrhea and chlamydia, in which a single swab can be collected and tested for both organisms with NAAT

methods. Additionally, non-invasive urine based diagnostic tests also using the NAAT technology have been licensed.

Laboratory Diagnosis of Gonorrhea and Chlamydia
New diagnostic techniques introduced in the last 10 years have changed management. Screening can occur outside traditional clinical arena (for example, in the city of Philadelphia there is a high-school based testing and treatment program). Various NAATs exist. They all have a very high sensitivity and specificity. The non-invasive specimens include First-void Urine, and a Vaginal or introital swab/wash. Combined NAAT assays for GC/CT costs have declined.

Treatment of Uncomplicated Gonococcal Infections, 2013
Intramuscular Ceftriaxone PLUS oral Azithromycin is the Recommended single-dose regimen. Always treat for chlamydial co-infection.

KEY POINTS: *Neisseria gonorrhoeae*

- Gram-negative diplococcus requiring special media (such as Thayer-Martin) to grow
- Antigenic variation allows it to evade immunity from prior exposure
- Strict human pathogen efficiently transmitted by infected secretions
- Urethritis (men) and cervicitis (women) but can infect other mucosal sites and cause invasive disease (disseminated gonococcal infection). Many of the clinical features overlap with Chlamydia.
- Diagnosis by a highly effective molecular test (NAAT) or culture
- Treatment by single dose injection of ceftriaxone plus oral azithromycin.

Chlamydia: Physiology and Structure
Chlamydia trachomatis is an obligate intracellular bacterium. It is a small Gram negative bacillus. *Chlamydia trachomatis* has several different serotypes that cause clinically distinct forms of disease. Serotypes A,B, and C cause the endemic eye disease in developing parts of the world known as trachoma. Serotypes D-K cause the genitourinary STD syndromes we commonly refer to as "chlamydia infection". Serovars L1-L3: cause a distinct STD called Lymphogranuloma venereum (LGV). *Chlamydia trachomatis* requires living tissues or cells for culture. This is labor intensive, and somewhat insensitive. As such, non-culture based diagnostics are gold standard.
C. trachomatis exists in 2 forms and has a unique life cycle:
Elementary body (EB): infectious form
Reticulate body (RB): noninfectious intracellular form that promotes replication

Chlamydia: Pathogenesis and Immunity
Receptors for the EB are only found on mucous membranes of: urethra, endocervix, endometrium, Fallopian tubes, anorectum, respiratory tract, and conjunctivae. The EB enters cell, replicates, infects other cells leading to cellular destruction, and an inflammatory host immune response that includes granulocytes, lymphocytes, and plasma cells. There is no lasting immunity; and re-infection is common. Inflammatory response with re-infection is strong and can lead to end organ damage (blindness, sterility).
Chlamydia: Epidemiology

Humans are the only natural hosts. The routes of transmission are the same as for gonorrhea and include direct mucosal contact with infected mucous membranes or fluids, and congenital. Chlamydia is much more widespread than gonorrhea, is the most commonly reported infectious disease in U.S. (4 million new cases annually), and adolescents are the cornerstone of the ongoing national epidemic. Risk factors for chlamydial infection include:
Young Age (Adolescence), Heterosexual, Increased Sexual Partners (2 or more)

Asymptomatic Chlamydia Infection: Pathogenesis and Immunity
Asymptomatic chlamydial infection leads to chronic infection. *C. trachomatis* can persist as long as 2 years in the female genital tract. This is known as "Silent PID". Asymptomatic infection is primary reason for of tubal infertility. In order to find and treat chlamydia, since so many patients are asymptomatic, SCREENING IS ESSENTIAL!!!

Chlamydia: Laboratory Diagnosis
Non-culture based diagnostics are preferred using the Nucleic acid amplification techniques (NAATs). A single swab for both GC and CT is now common.

Urine-based Diagnostics for Chlamydia and Gonorrhea
Benefits:
No pelvic exam, No urethral swab, Accuracy, Enhances screening opportunities, Enables data collection on asymptomatic population.
Drawbacks:
No substitute for sexual history-taking, No detection of resistance, Cannot test rectal/oropharyngeal specimens, and Amplification inhibitors can lead to false negatives.

Treatment of Uncomplicated Chlamydial Infection, 2013
Recommended Regimens:
- Azithromycin single dose
- Doxycycline (7 day regimen)

Both are equally efficacious

KEY POINTS: *Chlamydia trachomatis*

- Obligate intracellular pathogen, not cultured in clinical laboratories
- Two forms, Elementary bodies are the infectious form released by infected cells and Reticulate bodies are the intracellular form
- Prior exposure does not prevent reinfection
- Common human pathogen transmitted by infected secretions.
- Causes urethritis (men) and cervicitis (women). Asymptomatic infection in women contributes to PID and tubal infertility.
- Non-culture based diagnostic test (NAATs)
- Treatment with azithromycin (a macrolide) or doxycycline (a tetracycline)

Urethritis in Males
Signs and symptoms include dysuria, discharge, and burning. On physical exam the discharge varies in color and amount. One cannot determine the cause of the discharge by examination

alone. Gonorrhea tends to be more purulent, but can fool you. All patients should have a Gram stain if available. If not, then the patient should be treated for both gonorrhea and chlamydia. The diagnosis of gonococcal urethritis is made by Gram stain in which intracellular Gram negative diplococci are seen. The diagnosis should be confirmed with a culture or NAAT. If there are no intracellular gram negative diplococci, but there are 5 or more PMNs/oil field then the clinical diagnosis is nongonococcal urethritis (NGU). The most common cause of NGU is Chlamydia infection. However several other organisms can also cause NGU.
The etiologies of Nongonococcal Urethritis:

Chlamydia trachomatis	**50%**
Ureaplasma urealyticum?	<**10%**
Mycoplasma genitalium?	**<10%**
Trichomonas vaginalis	**<5%**
Herpes simplex	**<5%**

Epididymitis
Epididymitis presents as subacute onset of pain, swelling, and erythema of the scrotal sac; usually unilateral. On exam there is moderate to severe tenderness along with swelling and erythema. The clinician may not see a concurrent urethral discharge. In young sexually active males (<35) epididymitis is almost always caused by gonorrhea or chlamydia. Occasionally *E. coli* can be the cause in men who practice insertive anal sex. The diagnosis of epididymitis is usually a clinical one, though Gram stain/culture/NAAT test confirmation should be attempted.

Mucopurulent Cervicitis
Mucopurulent cervicitis in women is often asymptomatic, but manifestations can be seen on examination. It is caused by gonorrhea, chlamydia, both, and in rare circumstances neither will be identified. Symptoms, when present include discharge, dyspareunia, bleeding, dysuria, and/or lower abdominal pain. On exam one can see cervical friability (it bleeds easily with swab), edema, erythema, and/or an endocervical discharge. Sometimes there can be a completely normal cervical examination but the patient will test positive for gonorrhea or chlamydia. In these cases they should always be treated. The diagnosis of mucopurulent cervicitis is a clinical one. A positive swab test can be helpful (when the endocervix is swabbed, there is a yellow discharge on the swab tip). Gram stain has a low sensitivity here, and is not routinely recommended. Cultures/testing to confirm diagnosis should always be performed.

Pelvic Inflammatory Disease
PID includes inflammation of the upper genital tract and may manifest as a salpingitis, tubo-ovarian abscess, endometritis or peritonitis. There are an estimated 750,000 cases per year of symptomatic PID, and 1/3 of these cases may require inpatient care, and 10% will require a surgical procedure. One in 4 women with PID develops chronic sequelae. PID chronic sequelae include ectopic pregnancy (a 7-fold increased risk of this in the 1st pregnancy after diagnosis of PID); Infertility (a 15-20% risk of this with one episode of PID); and chronic pelvic pain (not well quantified, but leads to a fair number of hysterectomies). Data suggest that antimicrobial therapy has **no effect** on subsequent rates of sequelae. Therefore, the only way to impact on these chronic sequelae is to find the woman and diagnose her before she develops symptomatic PID. Thus, screening for gonorrhea and chlamydia are essential!

Microbiology of PID
N. gonorrhoeae and /or *C. trachomatis*
Anaerobes:
Bacteriodes spp.
Prevotella spp.
Peptococci and Peptostreptococci
Mobiluncus sp.
Gram-negative aerobes
Ureaplasma spp. and *Mycoplasma spp*.

Gonococcal Infections at Other Sites
Pharyngeal gonorrhea is often asymptomatic, non-exudative, and may be difficult to eradicate. Conjunctivitis presents dramatically with pain, erythema, and eye discharge. A Gram stain of the eye discharge usually provides the diagnosis. Perirectal gonorrhea presents with tenesmus, pain, and anal discharge. Exam shows friable mucosa with discharge.

Disseminated Gonococcal Infection
DGI is the result of gonococcal bacteremia. The organism disseminates from the GU tract into the bloodstream. Patients may present in one of two ways. The first presentation is as a Dermatitis-Arthritis syndrome. In this presentation of DGI patients have between 10-20 pustular, hemorrhagic lesions around small joints, and also have small joint tenosynovitis. IN the second presentation of SGI the patient presents with a septic, monoarticular arthritis, usually of the knee. In order to have the best chance of yielding a definitive microbiologic diagnosis, one must culture all exposure sites. Patients with DGI are treated with IV ceftriaxone initially, and changed to oral therapy after improved. A rare complication of DGI is gonococcal endocarditis.

Chlamydial Infections at Other Sites
Perirectal chlamydial infection can be seen in those practicing receptive anal sex. Chlamydial conjunctivitis can also occur and is always less symptomatic than gonococcal. The dysuria-pyuria syndrome is an important diagnosis to remember. Young sexually active women who present with urinary tract symptoms but have pyuria (WBC in their urine) but sterile urine cultures (this is known as sterile pyuria) should always have this diagnosis considered. Their sterile pyuria may be due to chlamydial (or less often, gonococcal) infection. A pelvic exam should always be performed and testing done for chlamydia and gonorrhea.

Lymphogranuloma Venereum
LGV is caused by L1-L3 serovars of *C. trachomatis.* It has always been endemic in Africa, India, SE Asia S. America and Caribbean.
Lymphogranuloma venereum
LGV presents as inguinal lymphadenopathy with or without proctitis. Proctitis has been seen in gay men and heterosexual women (direct inoculation or secondary spread from cervix). Pelvic nodes and lumbar lymph nodes are involved. LGV strains present with fever, tenesmus, bleeding and rectal pain. LGV can extend into colon.

Post-Infectious Sequelae-Reactive Arthritis

Is a post-inflammatory syndrome that is seen more commonly after chlamydia than gonorrhea, and can also be seen after bacterial gastroenteritis. The classic triad of symptoms are Arthritis, Conjunctivitis, and Urethritis. Skin lesions can also be seen and include keratoderma blenorrhagicum and a circinate balanitis.

Syphilis: Physiology and Structure

The etiologic agent of syphilis is *Treponema pallidum* subspecies *pallidum.* It is a corkscrew-shaped, helical, motile bacterium that cannot be cultured in vitro, is as long as a WBC (10-20 micrometers), and cannot be visualized under a light microscope.

Syphilis: Pathogenesis & Immunity

The organism penetrates and enters via skin or mucous membranes. The smaller the inoculum, the longer the incubation period (9-90 days) will be. Before any clinical signs/symptoms ever appear, the organism has traveled via the lymphatic system to regional lymph nodes, and then throughout the body via bloodstream. Invasion of the CNS occurs in > 30-40% of patients with 1^o or 2^o disease. Some spirochetes lodge at entry site, proliferate, sensitize lymphocytes and activate macrophages. The primary lesion (chancre) results at this site of inoculation. The chancre heals spontaneously, usually without scar, within 1-6 weeks, and serologic tests for syphilis may not be positive at this stage. Immunity develops in early latency. Eventually the host suppresses the secondary infection enough so that no lesions are clinically apparent. Latency: 60-85% of patients remain asymptomatic for the remainder of their lives. The other approximately 30% may progress to a tertiary stage of syphilis within a 2 to 40 year time period after initial infection. Immunity is present with chronic infection but lost after treatment

Syphilis Epidemiology

The routes of transmission for syphilis include:

- Direct contact with active lesions OR infectious mucous membranes (usually through sexual contact)
- Congenital
- Bloodborne (rare)

Individuals are most infectious and most capable of transmitting disease within the 1^{st} year of infection.

Syphilis: US Epidemiology

Syphilis rates decreased annually between 1993-2000. Since 2000, overall rates have been increasing. Rates in women and infants were on the decline in the early 2000s, but now are increasing as well. Additionally, there has been a major epidemic in men who have sex with men (MSM). Disease in U.S. is geographic (Southeastern US), urban (big cities), and in certain risk groups like MSM.

Primary Syphilis

The incubation period from time of inoculation to manifestation of primary infection is a mean of 21 days with a range 9-90 days. The time to infection depends on the size of the inoculum. The classic manifestation of primary syphilis is the Primary chancre. It is usually a Single **painless ulcer** at site of inoculation. The chancre has a smooth clean ulcer base, with borders that are raised, rolled, or indurated. Associate with the chancre, is **Painless** regional adenopathy.

There are no constitutional symptoms during this stage. Men usually see their chancre and present for evaluation. Women often are not diagnosed during this stage, because they do not see their chancre and it is asymptomatic.

Secondary Syphilis

During the secondary stage of syphilis the individual can manifest symptoms involving any organ system. It can look like many other diseases, and is described as having protean manifestations. The disease in this stage has also been called "The Great Imitator". Secondary syphilis manifestations occur 2-8 weeks after chancre. From the time of inoculation until manifestation of secondary syphilis the range of time is between 30-180 days. During this stage the spirochetes have disseminated, and the meninges have been seeded for some time.

Secondary Syphilis

Skin Manifestations:

- Rash: macular, papular, maculopapular, papulosquamous; diffuse; palmar-plantar
- Condylomata lata: grey-white or pink moist plaques found in intertriginous areas
- Alopecia

Constitutional symptoms:

- 70% patients affected
- Fever, malaise, anorexia, wt. loss, pharyngitis, myalgias

Mucous Patches

Painless generalized adenopathy

CNS disease:

- Headaches
- 1-2% develops aseptic meningitis
- Rarely can see cranial nerve involvement

Arthritis, hepatitis, osteitis all possible

Latent Syphilis

No clinical manifestations are evident during latent syphilis. The only evidence of infection is positive serology. Early latent syphilis is defined as asymptomatic (Asx) infection of < 1 year in duration. Late latent syphilis is defined as Asx infection greater than 1 year in duration, or of unknown duration. 25% of untreated early latent cases may relapse into another secondary syphilis episode. After 4 years without treatment, individuals are generally considered to be noninfectious (the exception is women who become pregnant who may still be capable of transmitting their syphilis infection to their unborn child). Individuals who have untreated latent syphilis are resistant to re-infection.

Tertiary syphilis

There are 3 types of tertiary syphilis: **gummatous**, **cardiovascular**, and **neurosyphilis**. Gummatous syphilis is characterized by the presence of gummatous lesions in the skeletal, spinal and mucosal areas. The eye and viscera (lung, stomach, liver, genitals, breast, brain, heart) can also be affected. Gummas are granuloma-like lesions. The spirochete is often not seen in the histologic specimens from gummas that are biopsied. The average time of onset of gummatous syphilis is 10-15 years.

Cardiovascular syphilis is characterized by the presence of a thoracic aortic aneurysm. Histologically, if biopsied there is an endarteritis of aortic vasovasorum that over time develops into a thinning of the aortic wall and eventual aneurysm formation. These aneurysms rarely rupture, but often track back into the heat leading to aortic insufficiency. The average time of onset for cardiovascular syphilis is 20-30 years.
Neurosyphilis is the most common manifestation of tertiary syphilis. There are several varied forms of tertiary neurosyphilis. The earliest to occur is meningovascular. This can be seen between 5-10 years after infection, and usually presents as stroke in a young person. Parenchymatous neurosyphilis presents as personality changes, dementia, delusions of grandeur, paranoia, and is the result of ongoing infection in the CNS. The average time of onset is around 20 years after infection.
Tabes dorsalis is the latest manifestation of neurosyphilis, occurring between 25-35 years after infection, and presenting with lightning pains down the legs, neuropathy, a characteristic gait due to demyelination of the dorsal spinal columns, and incontinence.
Other less common manifestations of neurosyphilis include various forms of eye disease and syphilitic otitis.

Laboratory Diagnosis of Syphilis

T. pallidum cannot be cultured in vitro. This limits diagnosis capabilities. A definitive diagnosis of syphilis can be made when there are active lesions of primary or secondary disease that can be scraped, and then examined under a Darkfield microscope. This is called Darkfield microscopy. Most laboratories no longer have a Darkfield microscope, and the majority of patients are diagnosed with latent disease, so in these settings the diagnosis is made through serologies. Serologic testing for syphilis is done in two steps!. First there is a screening test, performed using a nontreponemal test. If this test is positive, then a confirmatory test is ordered. The confirmatory tests are specific treponemal antibody tests.

Nontreponemal (Screening) tests include the RPR, and the VDRL. Less common nonspecific tests include the TRUST (Toluidine Red Unheated Serum Test), and the USR (Unheated Serum Reagin) tests. Nontreponemal tests measure IgM and IgG antibody directed against cardiolipin-lecithin cholesterol antigen. They are non specific for *T. pallidum*. The reaction may be microscopic (VDRL) or macroscopic (RPR). The advantages of the nontreponemal tests are that they are rapid, cheap, and quantitative (you can measure a titer, and then follow it over time to assess therapeutic response). Disadvantages include that they are insensitive in certain stages, and there can be several reasons to have biological false positive reactions to these tests.

The specific treponemal (Confirmatory) tests include the TPPA (formerly the MHA-TP) and FTA-Abs. tests for Syphilis. These tests measure antibody (IgM and IgG) directed against *T. pallidum* antigens by Immunofluorescence (FTA-Abs) or Hemagglutination (the TPPA/old MHA-TP and the TPHA). Tests depend on serum dilution and absorption for specificity. They remain reactive after adequate therapy and usually are positive for life. They cannot be quantitated, and thus cannot be followed to assess therapeutic response.

Newer Treponemal Tests:

Enzyme immunoassays, microbead assyas, and chemiluminescence assays all measure antibody production to T. pallidum. Some healthcare organizations are using these tests instead of traditional syphilis screening algorithms. This is called "reverse screening". It has drawbacks.

Treatment for Syphilis

Parenteral penicillin G is drug of choice for all stages of syphilis. It is the ONLY therapy with documented efficacy for neurosyphilis or for syphilis during pregnancy. In penicillin-allergic patients who are or non-pregnant, non-HIV-infected, doxycycline can be used as an alternative therapy.

KEY POINTS: *Treponema pallidum*

- Syphilis is caused by a spirochete that cannot be cultured
- Following direct contact it enters through the skin or mucus membranes and then disseminates
- Several stages of infection. Primary syphilis causes a painless ulcer (chancre). Secondary syphilis follows dissemination and is often diagnosed because of its characteristic cutaneous manifestations. Tertiary syphilis may follow a variable latent period and may involve gummas in a variety of tissues and cardiovascular and neurological diseases.
- Diagnosis by serology (nontreponemal screening test, RPR or VDRL, followed by more specific treponemal test if positive)
- Treatment-penicillin