Pathogenesis, clinical manifestations, and treatment of early syphilis

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INTRODUCTION — Syphilis is a chronic infection caused by the bacterium Treponema pallidum. The manifestations of disease are notoriously protean, occurring in any one individual in different stages over time [1].

The epidemiology, pathogenesis, clinical manifestations, diagnosis, and therapy of early syphilis will be reviewed here. Late syphilis and the pathophysiology, natural history, and serologic diagnosis of syphilis are discussed separately. Syphilis in the HIV-infected patient is discussed elsewhere. (See "Pathogenesis, clinical manifestations, and treatment of late syphilis" and "Pathophysiology, transmission, and natural history of syphilis" and "Diagnostic testing for syphilis" and "Epidemiology, clinical presentation, and diagnosis of syphilis in the HIV-infected patient".)

DEFINITIONS

Early syphilis — Early syphilis is defined as the stages of syphilis (primary, secondary, and early latent syphilis) that typically occur within the first year after acquisition of the infection.

Latent syphilis — Latent syphilis is characterized by asymptomatic infection with a normal physical examination in association with a positive serology. Latent syphilis is categorized as "early" or "late" depending on the established date of infection. Early latent syphilis infers infection within one year. All other cases are referred to as late latent syphilis or latent syphilis of unknown duration [2].

The importance of correct classification is related to the risk of transmission and duration of treatment:

- Public health agencies focus their contact tracing efforts on patients with early latent syphilis, since transmission is unlikely in late latency. The emphasis on identifying patients with early syphilis is also based on the concern that lesions may have been present earlier in the year, when sex partners may have been exposed. There is also the risk of recurrent lesions in the index patient, and therefore transmission, if untreated.
- The USPHS recommends a longer duration of therapy for patients with late latent syphilis. This recommendation is based upon the notion that the biology of the spirochete evolves over time. In late latent syphilis, T. pallidum is thought to have a slower metabolism and a more prolonged dividing time [2].

Unfortunately, misclassification of latent syphilis is common and can have a negative impact on appropriate treatment duration and on contact tracing [3,4]. Alternatively, some researchers have suggested that latent syphilis should be classified as "high-titer" or "low-titer" syphilis (based upon VDRL or RPR testing), since high nontreponemal titers are strongly associated with recent infection [3,5]. However, early latent syphilis cannot be reliably distinguished from late latent syphilis solely on the basis of nontreponemal titers [2]. (See "Pathophysiology, transmission, and natural history of syphilis" and "Diagnostic testing for syphilis".)

EPIDEMIOLOGY — Early syphilis is a reportable infection in the United States, so there are relatively accurate statistics on the incidence of new infections [2]. In the late 1980s and early 1990s there was a mini-epidemic of early syphilis that ultimately produced case rates that were higher than at any time since the introduction of penicillin. The number of cases peaked in 1990 (20.3 cases per 100,000 population) but subsequently fell to a new all time low in 2000, raising hopes for eradication (figure 1) [6,7].

Data from the United States Centers for Disease Control and Prevention (CDC) showed that the number of cases of early syphilis increased in 2001 for the first time since 1990, and this trend continued until 2010, when overall rates of primary and secondary syphilis decreased for the first time in a decade [8]. However, this decline in overall incidence is mainly attributable to a significant decrease in syphilis cases among women (27 percent) while rates among men increased by 1 percent from 2009 to 2010. Rates among men were highest among those aged 20 to 24 years, which is a marked shift from 2005, when rates were highest among men aged 35 to 39 years [8].

Rates of syphilis continue to be significantly higher in non-Hispanic blacks compared with non-Hispanic whites [8,9]. In particular, rates among black and Hispanic men aged 20 to 24 years were 15 times and 3 times the rate among white men of the same age group [8].

Syphilis remains an important problem in other areas of the world. The World Health Organization estimated that, in 1999, there were 100,000 new cases of syphilis in adults in North America, 140,000 in western Europe, 100,000 in eastern Europe, and central Asia, 370,000 in north Africa and the Middle East, and three to four million each in Latin America and the Caribbean, sub-Saharan Africa, and south and southeast Asia [10]. In China, a national surveillance program demonstrated that after the virtual eradication of syphilis in the 1960s to the 1980s, syphilis has reemerged with a total of 74,000 cases of primary and secondary syphilis diagnosed in 2005 alone [11].

Syphilis is associated with an increased risk for HIV acquisition and transmission [12]. (See 'Men who have sex with men' below and 'Women and minority groups' below and "Prevention of sexually transmitted infections".)

Men who have sex with men — Analyses of data from 2011 demonstrate that most cases of primary and secondary syphilis occur among MSM (figure 2) [9]. Risk factors for acquisition of early syphilis among MSM include HIV infection, combination methamphetamine and sildenafil use, and having acquired recent sexual partners from the Internet [13].

HIV-infected patients — There is a relatively high rate of HIV coinfection in persons with syphilis. Among the 6862 cases of primary and secondary syphilis documented in 2002 by the CDC, 25 percent occurred in persons coinfected with HIV; the risk group with the highest incidence rates was HIV-infected MSM (336 cases per 100,000) [14]. (See "Epidemiology, clinical presentation, and diagnosis of syphilis in the HIV-infected patient".)

Women and minority groups — In contrast, the incidence of early syphilis in women in the United States declined by 35 percent between 2000 and 2002 [15], a trend that unfortunately did not continue. Between 2005 and 2009, the number of cases of primary and secondary syphilis in women increased from 1339 to 2232. However, a 2010 report from the CDC demonstrated that rates of syphilis declined by 27 percent among women while rates continued to increase among men [8]. Unfortunately, reductions in rates of syphilis noted in African Americans earlier in the decade have not been sustained. During 2006 to 2010, rates among black men aged 20 to 24 years increased 134 percent; the magnitude of this rate increase (53 cases per 100,000 population) was the greatest of any sex, age group, or race/ethnicity group [8].

TRANSMISSION — Transmission of Treponema pallidum usually occurs via direct contact with an infectious lesion during sex. It is thought that the spirochete gains access via disrupted epithelium at sites of minor trauma [16]. The early lesions of primary and secondary syphilis including chancres, mucous patches, and condyloma lata, are very infectious. It has been estimated that transmission occurs in approximately one-third of patients exposed to these lesions [1].

Syphilis can also be spread by kissing or touching a person who has active lesions on the lips, oral cavity, breasts, or genitals. Transmission of syphilis has been identified in MSM who have reported oral sex as their only risk factor for acquisition [15].

The acquisition of syphilis through transfused blood is very rare because all donors are screened and T. pallidum cannot survive longer than 24 to 48 hours under the current blood bank storage conditions. The infection can also be acquired by passage through the placenta. (See "Syphilis in pregnancy".)

CLINICAL MANIFESTATIONS

Incubating syphilis — The median incubation period before clinical manifestations is 21 days (range 3 to 90 days).

Primary syphilis — A description of the pathophysiologic events occurring after acquisition of T. pallidum is described

separately. (See "Pathophysiology, transmission, and natural history of syphilis".) Briefly, after an average incubation period of two to three weeks, a papule, which is typically painless, appears at the site of inoculation. This soon ulcerates to produce the classic chancre of primary syphilis, a one to two centimeter ulcer with a raised, indurated margin (picture 1). The ulcer generally has a non-exudative base and is associated with mild to moderate regional lymphadenopathy that is often bilateral.

Such lesions usually occur on the genitalia, but occasionally patients may develop chancres at other sites of inoculation. These sites may include areas that may not be noticeable to the patient, including the posterior pharynx, anus, or vagina. Multiple chancres can occur infrequently, particularly in the setting of HIV infection. (See "Epidemiology, clinical presentation, and diagnosis of syphilis in the HIV-infected patient".)

Chancres heal spontaneously within three to six weeks even in the absence of treatment. Since the ulcer is painless, many patients do not seek medical attention, a feature that enhances the likelihood of transmission. The mechanism of healing is unknown, but is thought to be a consequence of local immune responses [17].

While the chancre represents initial local infection with T. pallidum, widespread dissemination of the spirochete also occurs early during the primary stage of infection.

Secondary syphilis — Weeks to a few months later, approximately 25 percent of individuals with untreated infection will develop a systemic illness that represents secondary syphilis [18]. Patients with secondary syphilis may not have a history of a preceding chancre since the primary lesion may go unnoticed. Secondary syphilis can also develop even when the primary chancre is still present; this may be more commonly seen in the HIV-infected patient. (See "Epidemiology, clinical presentation, and diagnosis of syphilis in the HIV-infected patient".)

Secondary syphilis can produce a wide variety of symptoms.

Rash — Rash is the most characteristic finding of secondary syphilis and can take any form, except vesicular lesions. The rash is classically a diffuse, symmetric macular or papular eruption involving the entire trunk and extremities (picture 2), including the palms and soles (picture 3) although localized lesions can also occur [19]. Individual lesions are discrete red or reddish-brown and measure 0.5 to 2 cm in diameter [17,20] (picture 4). They are often scaly but may be smooth and rarely pustular (eg, "pustular syphilids"). Pustular syphilis can take the form of small pustular syphilide, large pustular syphilide, flat pustular syphiloderm, and pustular-ulcerative syphilide (ie, malignant syphilis) [19]. Nodular lesions also may be seen. The involvement of the palms and soles is an important clue to the diagnosis of secondary syphilis.

Large, raised, gray to white lesions, involving warm, moist areas such as mucous membranes in the mouth and perineum, may develop in some patients during secondary syphilis. These are referred to as condyloma lata (picture 5 and picture 6). These lesions occur most often in areas proximate to the primary chancre and may reflect direct spread of organisms from the primary ulcer [17].

Systemic symptoms — Systemic symptoms include fever, headache, malaise, anorexia, sore throat, myalgias, and weight loss. These clinical manifestations probably reflect the brisk immunologic response resulting from widespread dissemination of T. pallidum.

Lymphadenopathy — Most patients with secondary syphilis have lymph node enlargement with palpable nodes present in the posterior cervical, axillary, inguinal and femoral regions (picture 7). The finding of epitrochlear nodes is particularly suggestive of the diagnosis. These nodes are generally minimally tender, firm, and rubbery in consistency.

Alopecia — So-called "moth-eaten" alopecia is occasionally seen among patients presenting with secondary syphilis (picture 8). This may be noted on the scalp, eyebrows, or beard, but is usually reversible with treatment.

Hepatitis — Syphilitis hepatitis is characterized by a high serum alkaline phosphatase level on laboratory examination, often with normal or only slightly abnormal transaminases. Mild clinical hepatitis resolves with treatment [21].

Gastrointestinal abnormalities — The gastrointestinal tract may become extensively infiltrated or ulcerated; this can be misdiagnosed as lymphoma.

Musculoskeletal abnormalities — Synovitis, osteitis, and periostitis can also occur, but usually resolve after treatment [22].

Renal abnormalities — Patients with syphilis can have mild transient albuminuria, nephrotic syndrome, or acute nephritis with hypertension and acute renal failure [23]. Pathologically, membranous glomerulonephritis or diffuse endocapillary glomerulonephritis, sometimes with crescents, can be seen. Resolution of renal abnormalities follows treatment for syphilis.

Neurologic abnormalities — Invasion of the cerebrospinal fluid (CSF) is common in early stages of the untreated disease. The pathogenesis of CNS syphilis and both its early and late clinical manifestations are described separately. (See "Neurosyphilis" and "Pathophysiology, transmission, and natural history of syphilis".)

Ocular abnormalities — Syphilis may be associated with anterior uveitis, posterior uveitis, or panuveitis, which is often granulomatous. The most common form of posterior uveitis is multifocal chorioretinitis, but other manifestations include retinal necrosis and optic neuritis. Onset of uveitis can also occur in tertiary syphilis as well [24].

DIAGNOSIS — As with all stages of the disease, diagnosis of early syphilis is complicated by the fact that the organism has never been cultivated in vitro. The chancre of primary syphilis is best diagnosed by darkfield microscopy, if available (picture 9), while secondary syphilis is reliably diagnosed by serologic testing. A complete discussion of the serologic diagnosis of early syphilis appears elsewhere. (See "Diagnostic testing for syphilis".)

Cerebrospinal fluid analysis is not routinely recommended in patients with primary or secondary syphilis since there is no evidence that treatment failures after benzathine penicillin are more common in early syphilis in patients with an abnormal CSF analysis [2]. The primary indications for lumbar puncture are clinical symptoms of meningitis or focal neurologic findings. (See "Neurosyphilis", section on 'Diagnosis'.)

Patients with latent syphilis should be evaluated clinically for evidence of tertiary disease (eg, aortitis and neurologic signs) and ocular disease (iritis and uveitis) [2]. This includes careful auscultation of the heart for evidence of murmurs and visual acuity screening for any eye disease. If history or physical examination suggests tertiary disease, echocardiography or formal ophthalmologic examination may be warranted. If neurologic disease is suspected, the patient should also have a cerebrospinal fluid examination [2]. (See "Neurosyphilis", section on 'Diagnosis'.)

The decision of whether a lumbar puncture should be performed in HIV-infected patients with syphilis is discussed elsewhere. (See "Epidemiology, clinical presentation, and diagnosis of syphilis in the HIV-infected patient".)

DIFFERENTIAL DIAGNOSIS — Among patients with a genital ulcer, the differential diagnosis includes syphilis, genital herpes, and chancroid. Non-infectious causes include drug eruptions and Behçet's disease (table 1). (See "Approach to the patient with genital ulcers".)

A diagnosis based upon history and physical examination alone is often inaccurate. Nonetheless, some findings are more common in certain infections [25]:

- Primary syphilis classically presents with a painless, indurated, clean-based ulcer, called a chancre.
- Genital herpes is characterized by multiple, shallow, tender ulcers that may be vesicular; a history of recurrent disease may be elicited. (See "Epidemiology, clinical manifestations, and diagnosis of genital herpes simplex virus infection".)
- The classic genital presentation of chancroid is with a deep, undermined, purulent ulcer that may be associated with painful inguinal lymphadenitis. (See "Chancroid".)

If the patient acquired syphilis through oral sex, a syphilitic chancre may be noted in the oral cavity on the buccal mucosa, tongue, or lips [15]. These syphilitic lesions can be misdiagnosed initially as herpetic or aphthous ulcers.

THERAPY — The efficacy of penicillin for the treatment of all stages of syphilis has been established over approximately 50 years of its clinical use [2,26,27]. Thus, the recommendation for the use of penicillin is not based on any clinical trial or observational data, but a long history of clinical use.

Antibiotic treatment of syphilis must be prolonged since T. pallidum divides slowly, averaging one doubling in vivo per day [28]. For this reason, long-acting penicillin preparations are the preferred drugs for the treatment of all stages of syphilis.

The following recommendations for the treatment of syphilis are consistent with the 2010 CDC guidelines [2].

Benzathine penicillin G — T. pallidum apparently remains highly sensitive to penicillin, and no resistance has been reported to date despite several decades of use. Little sensitivity testing has been done because the organism must be isolated in rabbits. Although few comparative trials have been performed, a long experience using long-acting depot penicillin preparations has proven very successful in the treatment of early and late stages of syphilis. A single dose of benzathine penicillin G (2.4 million units IM) provides low but persistent serum levels of penicillin and is standard therapy for primary, secondary, or early latent syphilis (table 2) [2,29]. (See 'Early syphilis' above.)

Late latent syphilis or latent syphilis of unknown duration requires three doses of 2.4 million units IM each at one-week intervals [2]. (See 'Latent syphilis of unknown duration' below.)

Early syphilis — Only the long-acting benzathine preparation should be used for treatment of early syphilis since low and continuous levels of penicillin are necessary for the elimination of treponemes [30]. Long-acting benzathine penicillin should only be given via the intramuscular route; intravenous administration has been associated with cardiopulmonary arrest and death [30].

Use of Bicillin L-A (2.4 million units of benzathine penicillin G) leads to detectable serum concentrations that are prolonged for up to 30 days. Use of Bicillin C-R (equal concentrations of procaine and benzathine penicillin G), results in serum drug levels for only seven days. Inadvertent use of this shorter-acting preparation in a Los Angeles STD clinic led to a large-scale public health investigation and retesting and retreatment of a significant number of patients [31]. The Bicillin C-R product is now labeled with a warning "not for the treatment of syphilis".

Latent syphilis of unknown duration — If it is possible to document that the patient was infected with T. pallidum within the last year (eg, had a chancre or nonreactive syphilis serology within the past year), it is appropriate to treat with a single dose of benzathine penicillin [2]. If not, the patient should be diagnosed with latent syphilis of unknown duration, or late latent syphilis, for which three doses of benzathine penicillin (2.4 million units IM) at weekly intervals are recommended (table 2) [2,29]. (See "Pathogenesis, clinical manifestations, and treatment of late syphilis".)

Jarisch-Herxheimer reaction — During penicillin therapy for syphilis, patients may develop the Jarisch-Herxheimer reaction, which is an acute febrile reaction frequently accompanied by headache and myalgias within the first 24 hours of treatment. This reaction is most common among patients with early syphilis [2]. Antipyretics can be used for symptomatic treatment. (See "Syphilis in pregnancy", section on 'Jarisch-Herxheimer reaction'.)

Penicillin allergic patients — Options for the treatment of early syphilis in penicillin allergic patients include tetracyclines, macrolides, or ceftriaxone, although the data are limited [2,28,32].

Although macrolides have the advantage of single dose administration (2 gram oral dose), reports of macrolide resistance have been a source of concern (see 'Macrolides' below). For this reason, we prefer doxycycline as our first line agent in the penicillin allergic nonpregnant patient. Azithromycin should be used only if adherence is a significant concern. When alternative agents to penicillin are used, close follow-up is essential.

The effectiveness of alternatives to penicillin in the treatment of latent syphilis has not been well documented. The 2010 CDC STD guidelines recommend the following [2]:

- Patients with early latent syphilis should respond to any of the options outlined above (tetracyclines, macrolides, or ceftriaxone).
- Patients with late latent syphilis, or latent syphilis of unknown duration, should be treated with doxycycline as the preferred agent (100 mg twice daily) for 28 days.

In certain circumstances, such as pregnancy, penicillin is preferred even in the penicillin-allergic patient. In these circumstances, penicillin desensitization needs to be considered. This topic is discussed in detail elsewhere. (See "Syphilis in pregnancy", section on 'Penicillin allergy' and "Allergy to penicillins".)

Tetracyclines — Patients with early syphilis who are allergic to penicillin may be treated with 14 days of either doxycycline (100 mg PO BID) or tetracycline (500 mg PO four times daily), but these regimens are less well studied than penicillin. Doxycycline can also be considered if there are local epidemiologic concerns regarding azithromycin resistance. (See 'Macrolides' below.)

Macrolides — The efficacy of a single 2 gram oral dose of azithromycin has been compared with 2.4 million units of penicillin G benzathine intramuscularly in two randomized controlled trials [33-35]:

- One trial evaluated 328 patients with primary, secondary, or latent syphilis [33]. Fifty-two percent of the study population was HIV-seropositive. The primary outcome was serologic cure, defined as a decrease in the RPR titer by at least two dilutions at nine months of follow-up. For patients with primary and secondary syphilis, resolution of lesions within two weeks after treatment was also required. The study demonstrated equivalent cure rates between the azithromycin and benzathine treatment groups (98 versus 95 percent), which did not vary by HIV status.

- A subsequent multicenter trial of 517 patients also showed equivalency of serologic cure rates for azithromycin and benzathine penicillin at six months, although the overall cure rates were much lower (78 versus 79 percent) [34]. HIV infection and pregnancy were exclusion criteria. Non-serious adverse events were more common in the azithromycin arm and were mainly gastrointestinal in nature.

Although these efficacy outcomes are encouraging, increasing reports of macrolide resistance have tempered enthusiasm for adopting azithromycin for the treatment of syphilis [36-39]. Studies demonstrate that the prevalence of azithromycin resistance varies widely depending on geography. For example, a substudy of the trial discussed above [34] found no evidence of azithromycin resistance in Madagascar, which is the country where the largest number of subjects was enrolled; this observation may have accounted for the overall good treatment outcomes [40]. However, in other areas, such as Shanghai, azithromycin resistance appears to be widespread [39].

Azithromycin resistance is due to an acquired 23S ribosomal RNA mutation [37]. This mutation has also been identified in Dublin, China, Seattle, and Baltimore [37]. All but one of these identified cases has occurred in MSM. It is unclear if these strains represent a single clone spread within sexual networks in North America and Ireland or multiple strains that have emerged independently due to drug pressure [41]. In a study of 58 T. pallidum isolates that were screened for the 23S mutation, individuals who were exposed to macrolides in the previous year were approximately twice as likely to have a resistant strain of syphilis compared with subjects who had not taken macrolides [42]. The data from this small study in Seattle suggest that increases in the prevalence of macrolide-resistant T. pallidum strains are due to antibiotic pressure and not the spread of a clonal strain among small, defined sexual networks.

Due to these concerns regarding the development of macrolide resistance, we recommend doxycycline as the first line agent for the penicillin-allergic patient with early syphilis. Macrolides should only be used in geographic areas with a low prevalence of macrolide resistance or in patients with a history of medication non-adherence. Patients who are treated with azithromycin should be instructed that careful follow-up is essential and that they should return to the physician if symptoms persist. (See 'Patient monitoring' below.) The efficacy of azithromycin in pregnancy or in latent syphilis of unknown duration has not been proven [2,38]. (See 'Tetracyclines' above and "Syphilis in pregnancy", section on 'Penicillin allergy'.)

Ceftriaxone — In the rabbit model, ceftriaxone has similar efficacy in the treatment of primary syphilis as penicillin [43]. Limited clinical data suggest that ceftriaxone may be effective for treatment of early latent and late latent syphilis; the optimal dose and duration have not been defined. Some specialists recommend 1 gram daily for 8 to 10 days [2].

Some patients who are allergic to penicillin may also be allergic to ceftriaxone; this agent should not be used in patients with a history of immediate hypersensitivity reactions to beta-lactams due to potential cross-reactivity.

PATIENT MONITORING — All patients should be reexamined clinically and serologically at six and 12 months after treatment [2,44]. A fourfold reduction in titer of the nontreponemal antibody test (eg, from 1:16 to 1:4) is considered evidence of an appropriate response.

Unfortunately, some 15 percent of persons with early syphilis who receive recommended therapy do not achieve this

fourfold decline at one year after treatment [45]. It is not clear that this represents treatment failure since most such patients do not present with subsequent clinical findings. (See "Laboratory monitoring of patients undergoing treatment for syphilis".)

Patients who do not have an appropriate decline in titer are managed by giving another course of benzathine penicillin (2.4 million units IM weekly for three weeks) and making sure all sexual contacts are also treated to decrease the risk of reinfection [2]. The Centers for Disease Control and Prevention also recommends HIV testing and lumbar puncture in this situation [2]. (See "Pathogenesis, clinical manifestations, and treatment of late syphilis".)

SCREENING AND PREVENTION — There is no vaccine for syphilis. Patients should be educated that safer sex practices are vital for the prevention of infection. This includes barriers methods for vaginal, anal, and oral sex [15]. (See "Screening for sexually transmitted infections" and "Prevention of sexually transmitted infections".)

Tracing and treating the sexual contacts of patients with infectious syphilis has been highly effective in limiting the further spread of the disease in communities. Contacts are treated with the same regimens as infected patients according to the following recommendations from the 2010 CDC guidelines on the treatment of STDs [2]:

- Persons who were exposed within 90 days preceding the diagnosis of primary, secondary or early latent syphilis in a sex partner might be infected even if seronegative; therefore, such persons should be treated presumptively.
- Persons who were exposed >90 days before the diagnosis of syphilis in a sex partner should be treated presumptively if follow-up is uncertain.
- Long-term sex partners of patients who have latent syphilis should be evaluated clinically and serologically for syphilis and treated on the basis of the evaluation.

All patients with HIV infection should be tested for syphilis, and **all** patients with early syphilis should be tested for HIV. In areas of high HIV seroprevalence, HIV-seronegative patients with primary syphilis should be rescreened for HIV in three months [2].

The United States Preventive Services Task Force (USPSTF) issued updated guidelines for syphilis screening in the summer of 2004 [46]. A review of recent evidence increased the strength of support for the strategy of screening all pregnant women and people at higher risk of acquiring syphilis (MSM who engage in high risk behaviors, commercial sex workers, persons who exchange sex for drugs, and those in adult correctional facilities). The task force recommended against routine screening of asymptomatic persons who are not at increased risk of syphilis, since most positive tests in this setting represent false positive and can lead to unnecessary anxiety for patients, as well as increased costs and potential harm from inappropriate antibiotic use.

Mass treatment with azithromycin (1.8 g PO once) was attempted in Vancouver, British Columbia in 2000 to address a dramatic increase in heterosexual syphilis cases associated with sex workers [47]. The rates of syphilis fell significantly from a monthly mean of 10.2 before the treatment to 6.7 for the six months after mass treatment, but subsequently rose to higher than expected rates in 2001. Increasing evidence of resistance to azithromycin suggests this strategy is not recommended [36,37].

INFORMATION FOR PATIENTS — UpToDate offers two types of patient education materials, “The Basics” and “Beyond the Basics.” The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on “patient info” and the keyword(s) of interest.)

- Basics topic (see "Patient information: Syphilis (The Basics)")

SUMMARY AND RECOMMENDATIONS

Definitions

- Syphilis is a chronic infection caused by the bacterium Treponema pallidum. Early syphilis is defined as the stages of syphilis (primary, secondary, and early latent syphilis) that typically occur within the first year after acquisition of the infection.
- Latent syphilis is characterized by asymptomatic infection with a normal physical examination in association with a positive serology. (See 'Definitions' above.)

Clinical manifestations

- In primary syphilis, the classic lesion is a painless ulcer associated with mild to moderate regional lymphadenopathy. (See 'Clinical manifestations' above.)
- Patients with secondary syphilis have marked systemic symptoms, such as malaise, fever, headache, and rash. (See 'Clinical manifestations' above.)

Treatment — The following antibiotics have activity against syphilis: penicillin, doxycycline, azithromycin, and ceftriaxone. For patients with early syphilis, we recommend penicillin as the drug of choice (**Grade 1B**). We agree with the 2006 STD treatment guidelines issued by the CDC, as summarized below:

- For patients with primary or early latent syphilis, benzathine penicillin G (formulated as Bicillin L-A at a dose of 2.4 million units) should be administered as a single dose.
- Patients with late latent syphilis or syphilis of unknown duration should be treated with three doses of benzathine penicillin (formulated only as Bicillin L-A at a dose of 2.4 million units) at weekly intervals. (See 'Therapy' above.)
- Long-acting benzathine penicillin should only be given via the intramuscular route; intravenous administration has been associated with cardiopulmonary arrest and death. (See 'Therapy' above.)
- In patients who develop fever, headache, and myalgias consistent with Jarisch-Herxheimer reaction, antipyretics can be used for symptomatic relief. (See 'Jarisch-Herxheimer reaction' above.)
- In patients with severe penicillin allergy, alternative agents for the treatment of syphilis include doxycycline or azithromycin. We suggest doxycycline (100 mg twice daily for 14 days) as the preferred agent due to increasing reports of azithromycin resistance (**Grade 2B**). If there are concerns about medication nonadherence, we suggest a single dose of azithromycin (two grams) (**Grade 2B**). Prior to azithromycin therapy, local public health officials should be consulted to determine local macrolide resistance patterns. When alternative agents to penicillin are used, close follow-up is essential.

Patient monitoring

- All patients should be reexamined clinically and serologically at six and 12 months after treatment. A fourfold reduction in titer of the nontreponemal antibody test is considered evidence of an appropriate response. (See 'Patient monitoring' above.)
- In patients who do not have an appropriate decline in titer, we suggest another course of benzathine penicillin (2.4 million units IM for three weeks) for possible treatment failure (**Grade 2C**). All sexual contacts should be treated. The CDC also recommends HIV testing and diagnostic lumbar puncture for these patients. (See 'Patient monitoring' above.)

Screening and prevention

- All patients with early syphilis should be tested for HIV. (See 'Screening and prevention' above.)

- Tracing and treating the sexual contacts of patients with infectious syphilis decreases transmission. Contacts are treated with the same regimens as infected patients. (See 'Screening and prevention' above.)

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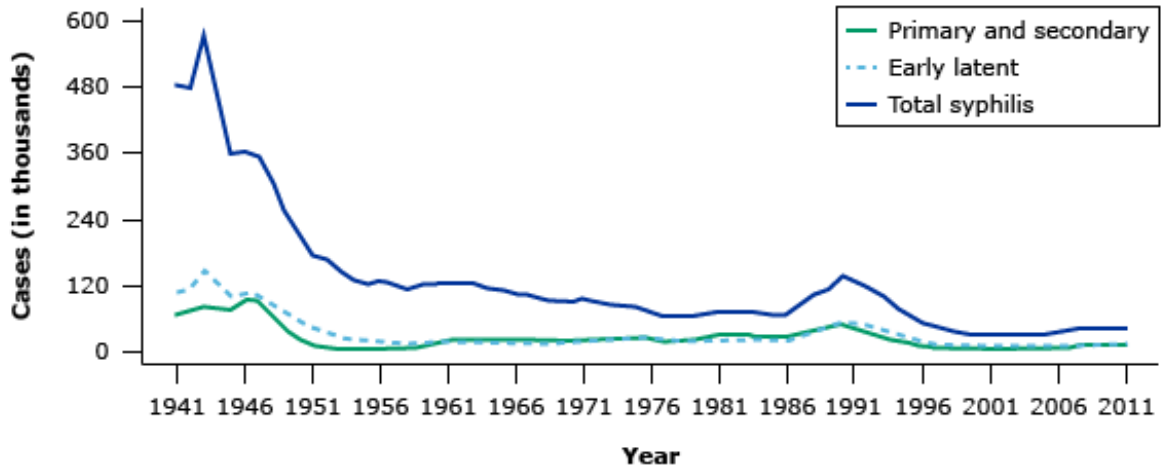
Topic 7594 Version 15.0

GRAPHICS

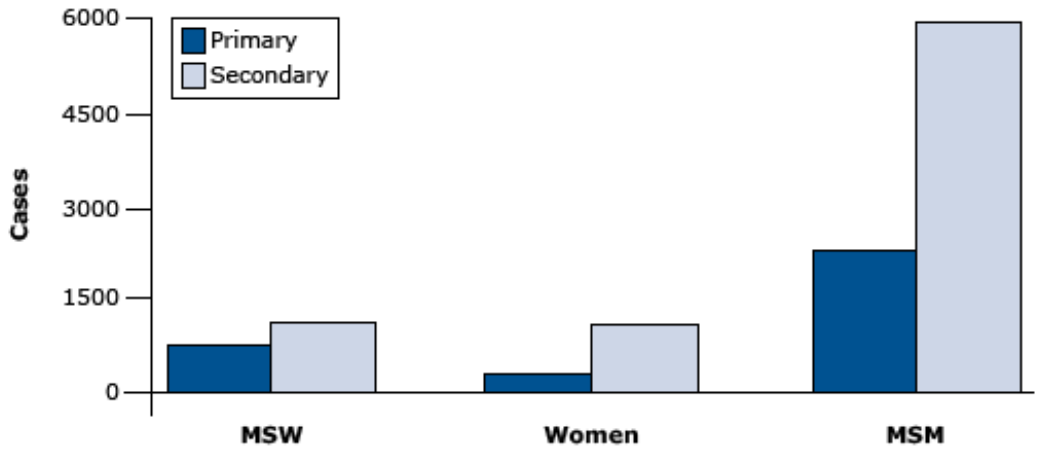
Syphilis - reported cases by stage of infection, United States, 1941-2011



Reproduced from: Centers for Disease Control and Prevention (CDC). Sexually transmitted disease surveillance - 2011. Available at: http://www.cdc.gov/std/stats11/Surv2011.pdf (Accessed on April 10, 2013).

Graphic 59772 Version 2.0

Primary and secondary syphilis - reported cases* by stage, sex, and sexual behavior, United States, 2011

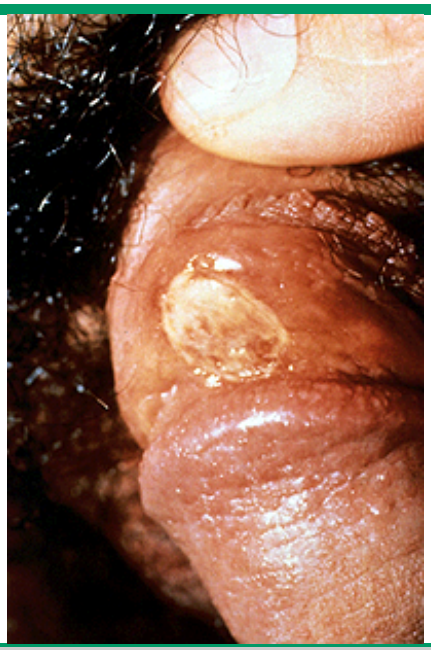


MSW: men who have sex with women only; MSM: men who have sex with men.
* Of the reported male cases of primary and secondary syphilis, 17 percent were missing sex of sex partner information.

Reproduced from: Centers for Disease Control and Prevention (CDC). Sexually transmitted disease surveillance - 2011. Available at: http://www.cdc.gov/std/stats11/Surv2011.pdf (Accessed on April 10, 2013).

Graphic 88975 Version 1.0

Primary syphilis: Penile chancre

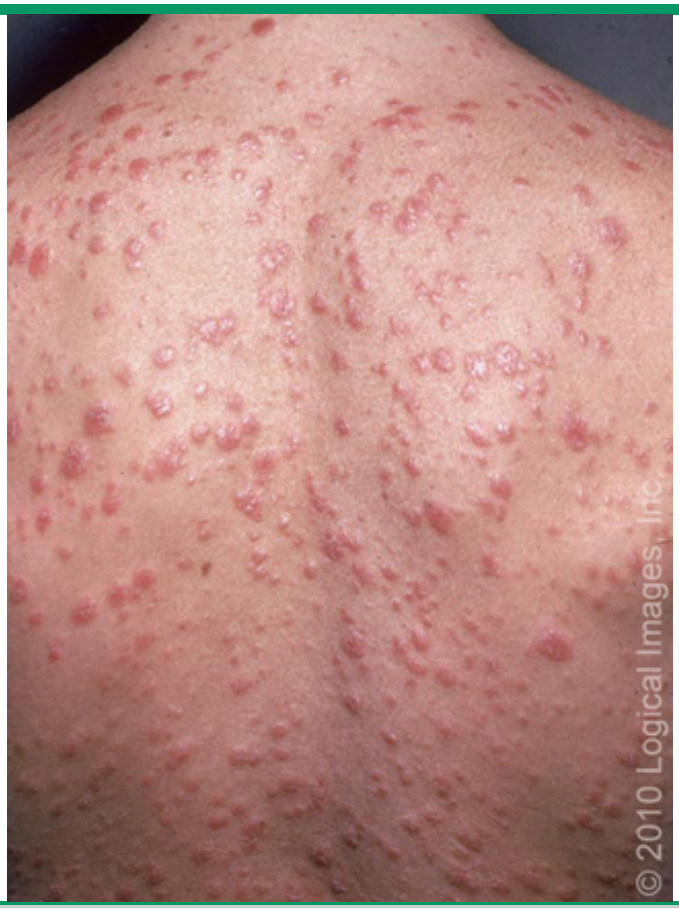


A chancre due to syphilis is an ulcerative lesion that is often painless and has an indurated character. Chancres arise at the site of initial inoculation of the organism.

Courtesy of Charles B Hicks, MD.

Graphic 75291 Version 3.0

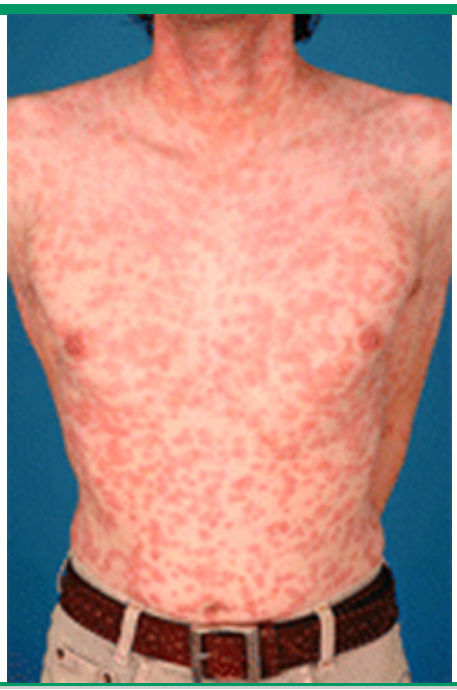
Secondary syphilis



Multiple slightly scaly erythematous papules are present on the trunk of this patient with papular secondary syphilis.

Graphic 60313 Version 3.0

Trunk rash secondary syphilis



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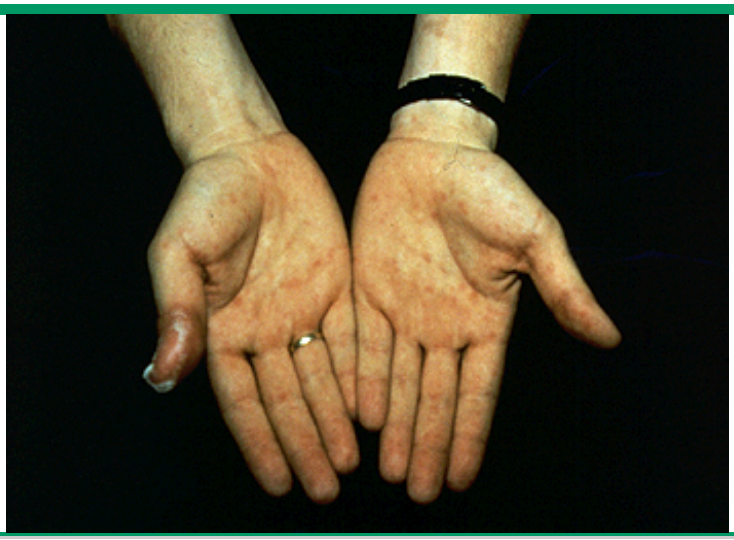
Graphic 79451 Version 1.0

Secondary syphilis: Rash

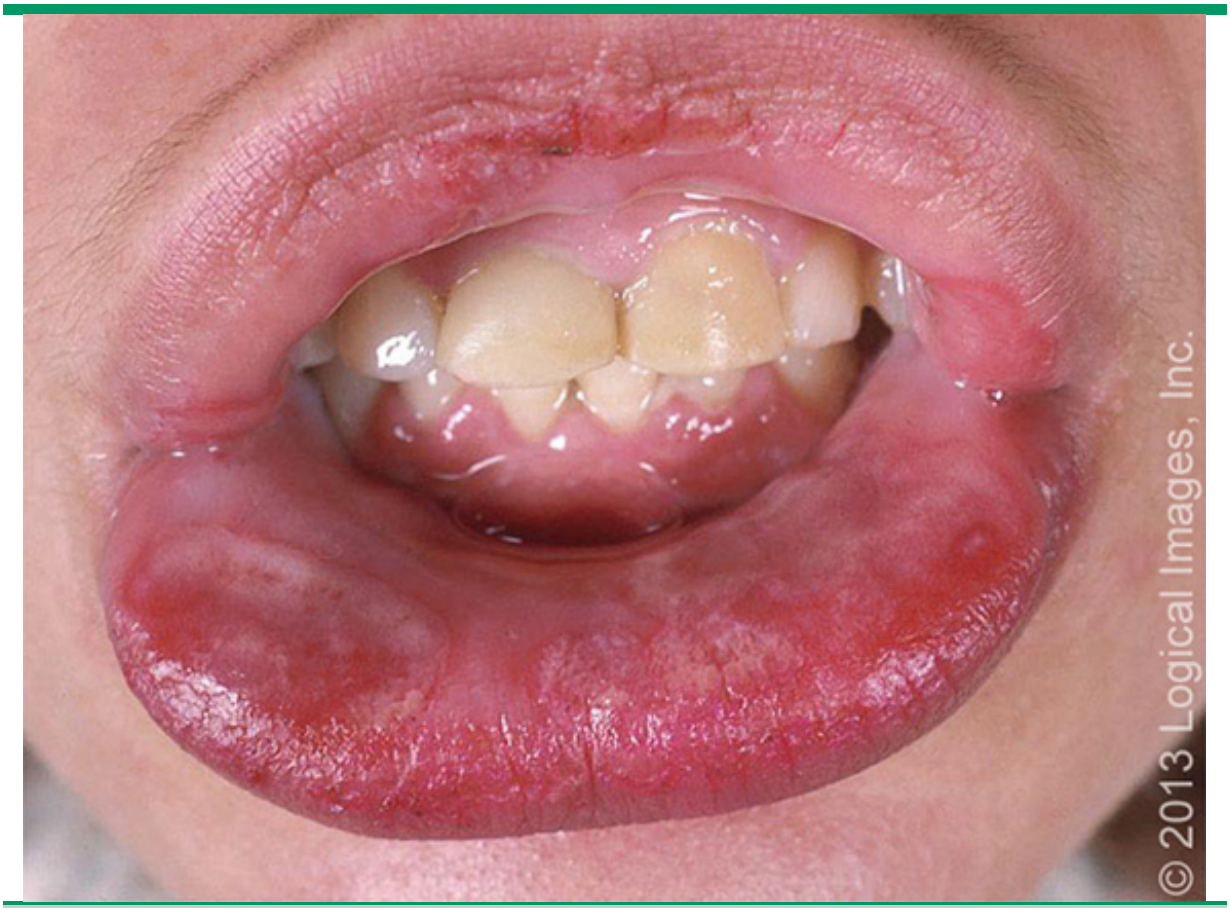


The rash of secondary syphilis characteristically involves the palms and soles. It may have a variety of appearances but is usually pigmented and macular.

Courtesy of Charles B Hicks, MD.

Graphic 68877 Version 4.0

Secondary syphilis: Mucous patch



The mucous patches of secondary syphilis may appear on a variety of mucous membranes. They are teeming with organisms and are therefore highly infectious.

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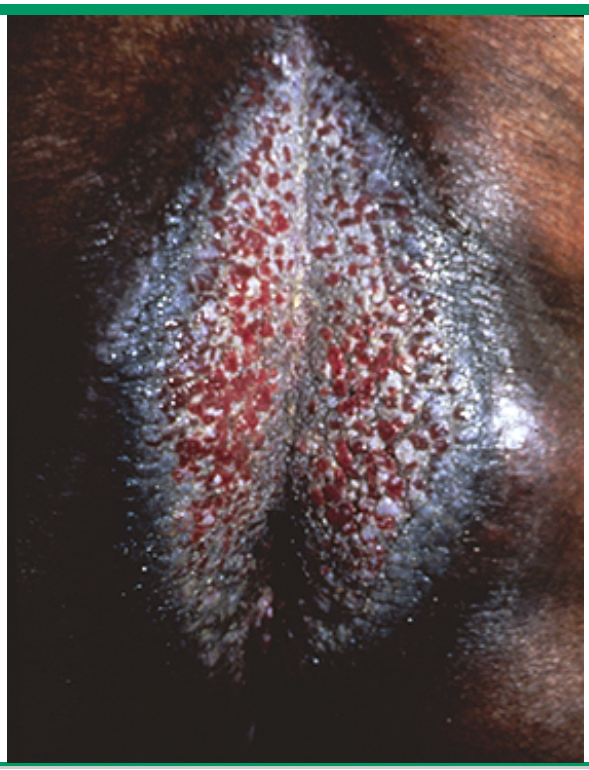
Graphic 66087 Version 10.0

Condyloma lata in the perineal region of a woman with secondary syphilis

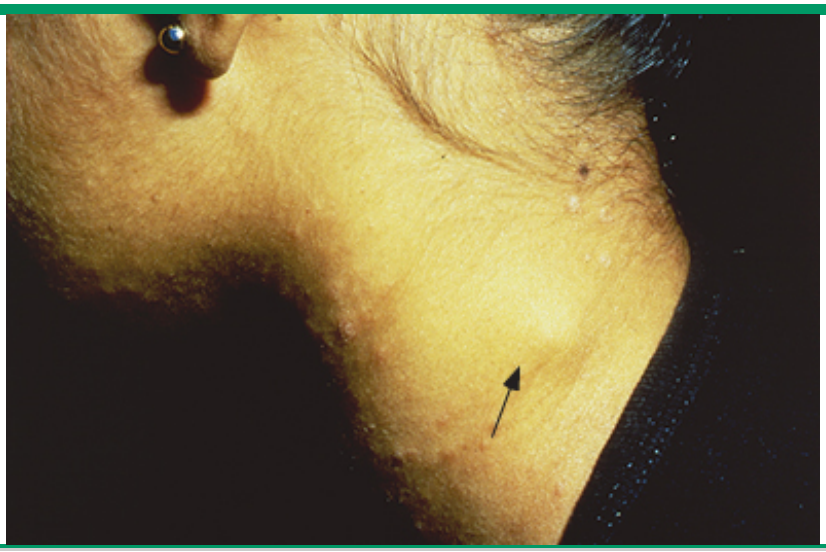


Numerous organisms are generally present in these lesions, which makes them highly infectious.

Courtesy of Charles Hicks, MD.

Graphic 63924 Version 1.0

Cervical lymph node in secondary syphilis

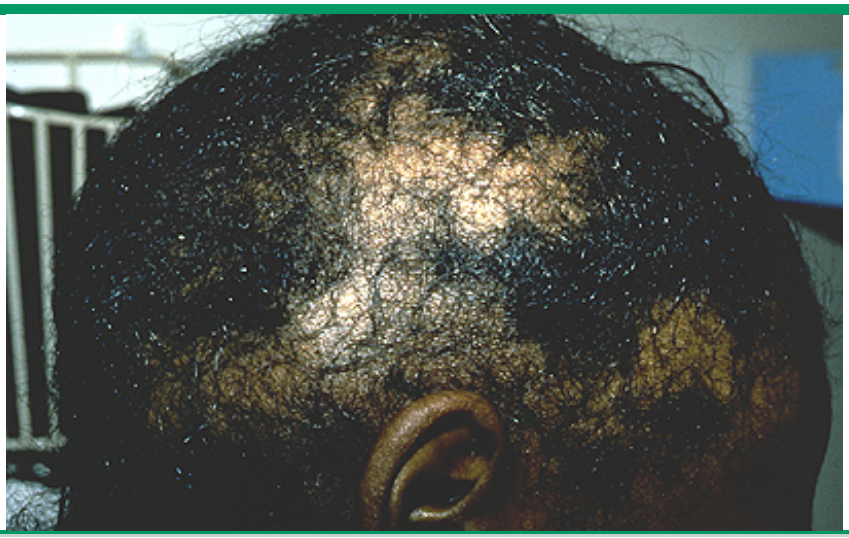


Such nodes (arrow) may be found in various locations and are usually firm, non-tender, and "rubbery" in consistency.

Courtesy of Charles Hicks, MD.

Graphic 59275 Version 1.0

Patchy alopecia in secondary syphilis

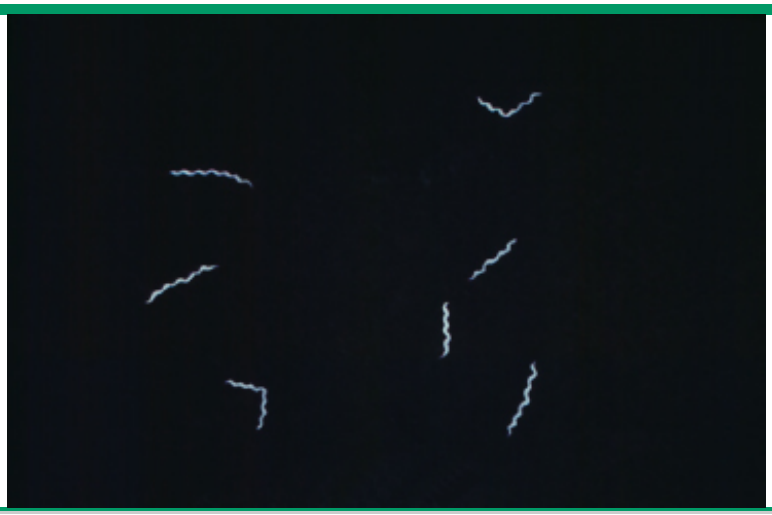


Hair loss associated with secondary syphilis is usually patchy, producing a so-called moth-eaten appearance.

Courtesy of Charles Hicks, MD.

Graphic 52213 Version 1.0

Treponema pallidum: darkfield microscopy



Dark field examination of exudate from a penile ulcer (x1000) in a patient with syphilis. The spirochete Treponema pallidum, which is too small to be seen using ordinary microscopy, appears as a delicate spiral rod when dark field illumination is employed.

Courtesy of Harriet Provine.

Graphic 63806 Version 3.0

Clinical characteristics of infectious causes of genital ulcer disease

GUD syndrome	Etiologic agent	Classic ulcer characteristics	Incubation	Pain	Adenopathy
HSV	HSV type 2 in most cases, HSV-1 is less common	Multiple small grouped ulcers; erythematous base. Occasionally, single lesions/fissures can be seen	2-7 days	Usually painful; can be painless or pruritic	Reactive painful nodes common
		Vesicles can open forming shallow ulcers/erosions which may coalesce			
Syphilis	Treponema pallidum	Indurated, smooth firm borders	7-90 days	Usually painless; rarely can be painful	Firm, rubbery nodes
		Clean base			Not tender
		Heals spontaneously			Regional
		Usually singular, although multiple chancres can occur			Discrete
Chancroid	Haemophilus ducreyi	Sharply circumscribed or irregular, ragged undermined edges	3-10 days	Marked	50 percent with inguinal adenopathy
		Not indurated			Usually unilateral
		Base may have gray or yellow exudate			Often painful
		Multiple ulcers			May suppurate/rupture
LGV	Chlamydia trachomatis L1-L3	Usually not observed	5-21 days	Usually painless	More common in males
		Small and shallow			Matted clusters
		Rapid spontaneous healing			Unilateral or often bilateral

					Large painful fluctuant "buboe"
					Painful groove sign
					Sinus tracts common
Granuloma inguinale	Calymmatobacterium granulomatis	Extensive, progressive	7-90 days	Usually painless	Pseudobuboes
		Granulation-like tissue			
		Rolled edges			

Graphic 81735 Version 1.0

Treatment options for syphilis

Early (primary, secondary, or latent less than one year)
Drugs of choice
Penicillin G benzathine 2.4 million units IM once*
Alternatives
Doxycycline• 100 mg oral twice daily for 14 days
Late (more than one year's duration, cardiovascular, gumma, late-onset)
Drugs of choice
Penicillin G benzathine 2.4 million units IM weekly for three weeks
Alternatives
Doxycycline• 100 mg oral twice daily for four weeks
Neurosyphilis$^{\Delta}$
Drugs of choice
Penicillin G 3 to 4 million units IV every four hours or 24 million units continuous IV infusion for 10 to 14 days **OR**
Penicillin G procaine 2.4 million units IM daily **plus** probenecid 500 mg four times daily oral, both for 10 to 14 days
Alternatives
Ceftriaxone 2 g IV once daily for 10 to 14 days
Congenital
Drugs of choice
Penicillin G 50,000 units/kg every 8 to 12 hours for 10 to 14 days **OR**
Penicillin G procaine 50,000 units/kg IM daily for 10 to 14 days

* Some experts recommend a repeat dose after seven days, especially in patients with HIV infection or pregnant women.
• Not recommended in pregnancy.
Δ Patients allergic to penicillin should be desensitized and treated with penicillin.

Adapted from: Drugs for sexually transmitted diseases. Treat Guidel Med Lett 2004; 2:67.

Graphic 50435 Version 2.0

Disclosures

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