Sporotrichosis

Sporothrix schenckii is a dimorphic fungus found most often in soil, living plants, or plant debris. Although found worldwide, most reported infections are from North and South America and Japan. Infection can occur after direct contact with plants, such as roses and sphagnum moss. Direct inoculation of the organism into the skin or subcutaneous tissue manifests as fixed, "plaque-like" cutaneous sporotrichosis or as lymphocutaneous sporotrichosis presenting as papular lesions along lymphatic channels proximal to the inoculation site. Extracutaneous infection (osteoarticular, pulmonary, ocular, or disseminated) can occur in immunocompromised hosts.

Diagnosis requires culture of the organism from affected tissues. Treatment is with itraconazole and should extend for 2 to 4 weeks after lesions have resolved.

KEY POINTS

- Sporotrichosis is an infection of cutaneous and lymphocutaneous tissues and usually is caused by direct contact with plants; extracutaneous infection can occur in immunocompromised hosts.
- Itraconazole is the preferred treatment for cutaneous and lymphocutaneous sporotrichosis.

Mucormycosis

Mucormycosis (formerly zygomycosis) is the third most frequent cause of invasive fungal infections in immunocompromised hosts but is rarely seen in immunocompetent hosts. Particularly at risk are patients with neutropenia, diabetes mellitus, and acidosis. The most common mucormycetes are *Rhizopus arrhizus* and *Mucor* species. These fungi are commonly found in the environment on decaying organic debris, including fruit, bread, and soil.

Infection is acute and rapidly fatal, even with early diagnosis and treatment. Major blood vessels are invaded, with ensuing ischemia, necrosis, and infarction of adjacent tissues. Mucormycosis has five major clinical forms: (1) rhinocerebral; (2) pulmonary; (3) abdominal, pelvic, gastric, gastrointestinal; (4) primary cutaneous; and (5) disseminated.

Because laboratory studies are nonspecific, diagnosis relies on a high index of suspicion in a host with appropriate risk factors and evidence of tissue invasion, including the characteristic appearance of broad, nonseptate hyphae with acute-angle branches. Serologic tests and blood cultures offer no diagnostic benefit.

Treatment requires reversal of any predisposing condition, extensive surgical removal of affected tissue, and early antifungal therapy. Initial treatment is high-dose liposomal amphotericin B, with later de-escalation to posaconazole or isavuconazole. If amphotericin B is not tolerated, initial therapy with one of the azoles is warranted. Mortality rates remain as high as 60% to 80%, even with therapy.

KEY POINTS

- Mucormycosis is acute and rapidly fatal, even with early diagnosis and treatment.
- Because laboratory studies are nonspecific, diagnosis relies on a high index of suspicion; serologic tests and blood cultures offer no diagnostic benefit.
- Treatment requires reversal of any predisposing condition, extensive surgical removal of affected tissue, and initial antifungal therapy with high-dose liposomal amphotericin B.

Sexually Transmitted Infections

Introduction

Sexually transmitted infections (STIs) occur most commonly in adolescents, young adults, and men who have sex with men (MSM), but STIs affect all demographics. Most infections are asymptomatic, so it is imperative that a detailed sexual history, including sexual practices, be obtained to understand individual risk. STI risk factors include a new partner, more than one current partner, a partner with an STI, or a partner who has concurrent partners. Particularly high-risk populations include persons attending STI clinics and MSM.

Unrecognized or inadequately treated upper genitourinary tract infection is a preventable cause of infertility in women. Evidence-based guidelines for the evaluation and management of STIs are available from the World Health Organization and the Centers for Disease Control and Prevention (CDC); the CDC guidelines are recommended for use in the United States. Any patient diagnosed with an STI should be evaluated for other STIs, including HIV, and receive risk reduction counseling.

Chlamydia trachomatis Infection

Chlamydia trachomatis is the most commonly reported bacterial STI in the United States, and incidence has increased steadily over the past two decades. Screening of all sexually active women younger than 25 years is recommended. Women aged 25 years and older should be screened if they have STI risk factors. The U.S. Preventive Services Task Force (USPSTF) concluded that evidence is insufficient to support routine screening in men; the CDC recommends screening men in settings or populations with high prevalence or burden of disease (MSM, STI clinics).

Nucleic acid amplification testing (NAAT) is preferred for screening and diagnosis. First-catch urine (for men and women) and endocervical (for women) or urethral (for men) swabs can be used. NAAT of urine samples for *C. trachomatis* and *Neisseria gonorrhoeae* has been shown to have a

sensitivity and specificity nearly identical to tests obtained from urethral and endocervical samples. In addition to cervicitis and urethritis, chlamydia may cause oropharyngeal and rectal infection, and these sites should be evaluated based on history of sexual practices. Although commercially available, NAAT may not be FDA cleared for testing extragenital sites; laboratories can provide this testing if they have confirmed internal criteria for validity of test results.

Treatment of clinical syndromes caused by *C. trachomatis* is outlined in **Table 32**. Test of cure is not recommended,

TABLE 32. Treatment of *Chlamydia trachomatis* and *Neisseria gonorrhoeae* Infections and Their Complications

Clinical Syndrome	Preferred Regimen	Alternate Regimen
Cervicitis and urethritis (empiric therapy)	Ceftriaxone, 250 mg IM single dose, plus azithromycin, 1 g PO single dose (preferred), *or* doxycycline[a], 100 mg PO twice daily for 7 d (only if azithromycin cannot be used)	Cefixime, 400 mg PO single dose, plus azithromycin, 1 g PO single dose (preferred), *or* doxycycline, 100 mg PO twice daily for 7 d
Chlamydia cervicitis, urethritis, or proctitis	Azithromycin, 1 g PO single dose, *or* doxycycline, 100 mg PO twice daily for 7 d (21 d if *C. trachomatis* LGV serovars suspected or confirmed)	Erythromycin base, 500 mg PO four times daily, *or* erythromycin ethylsuccinate, 800 mg PO four times daily, *or* levofloxacin, 500 mg PO daily, *or* ofloxacin, 300 mg PO twice daily for 7 d
Gonococcal cervicitis, urethritis, or proctitis and pharyngeal infection[b]	Ceftriaxone, 250 mg IM single dose, plus azithromycin, 1 g PO single dose (preferred), *or* doxycycline, 100 mg PO twice daily for 7 d (only if azithromycin cannot be used)	Cefixime[c], 400 mg PO single dose, plus azithromycin, 1 g PO single dose (preferred), *or* doxycycline, 100 mg PO twice daily for 7 d Test of cure 2 weeks after treatment for pharyngeal gonorrhea treated with an alternate regimen
Disseminated gonococcal infection[d]	Ceftriaxone, 1 g IM or IV every 24 h, plus azithromycin, 1 g PO single dose	Cefotaxime, 1 g IV every 8 h, *or* ceftizoxime[e], 1 g IV every 8 h, plus azithromycin, 1 g PO single dose
Pelvic inflammatory disease		
Parenteral therapy[f]	Cefotetan, 2 g IV every 12 h, or cefoxitin, 2 g IV every 6 h, plus doxycycline, 100 mg IV or PO every 12 h OR Clindamycin, 900 mg IV every 8 h, plus gentamicin, 2 mg/kg IV loading dose followed by 1.5 mg/kg IV every 8 hours or a single daily dose of 3-5 mg/kg/d	Ampicillin-sulbactam, 3 g IV every 6 h, plus doxycycline, 100 mg IV or PO every 12 h
Oral/IM therapy	Ceftriaxone, 250 mg IM single dose, plus doxycycline, 100 mg PO twice daily for 14 d, with or without metronidazole, 500 mg PO twice daily for 14 d, *or* cefoxitin, 2 g IM single dose, with probenecid, 1 g PO, plus doxycycline, 100 mg PO every 12 h for 14 d, with or without metronidazole, 500 mg PO twice daily for 14 d	
Epididymitis	Ceftriaxone, 250 mg IM single dose, plus doxycycline, 100 mg PO twice daily for 10 d if infection most likely due to chlamydia/gonorrhea Ceftriaxone, 250 mg IM single dose, plus levofloxacin, 500 mg PO once daily, or ofloxacin, 300 mg PO twice daily for 10 d if infection might be caused by chlamydia/gonorrhea and enteric organisms (insertive anal intercourse) Levofloxacin, 500 mg PO once daily, or ofloxacin, 300 mg PO twice daily, for 10 d if infection most likely caused by enteric organisms	

IM = intramuscularly; IV = intravenously; LGV = lymphogranuloma venereum; PO = orally.

[a]Doxycyline should be avoided or used with caution in pregnant patients.

[b]Treatment for possible chlamydial infection is recommended for all patients diagnosed with gonorrhea. Currently recommended treatment regimens for gonorrhea provide this coverage.

[c]Cefixime should be used only if ceftriaxone is unavailable because oral cephalosporin resistance to *N. gonorrhoeae* has been increasingly reported.

[d]For arthritis-dermatitis syndrome, parenteral therapy should be used until 24 to 48 hours after substantial clinical improvement and then switched to an oral therapy based on susceptibility results for a total of 7 to 10 days of treatment. Parenteral therapy is required for the entire course of treatment for meningitis (10 to 14 days) and endocarditis (at least 28 days).

[e]Not available in the United States.

[f]Patients can be switched to oral therapy within 24 to 48 hours of clinical improvement using doxycycline, 100 mg PO twice daily, with or without metronidazole, 500 mg PO twice daily, to complete a total of 14 days of therapy.

except in pregnancy. Because of the high risk of repeat infection, men and women should be retested after 3 months or the next time they are seen for medical care.

KEY POINTS

- First-catch urine (or genital swab) nucleic acid amplification testing is the preferred screening and diagnostic method for *Chlamydia trachomatis* infection.
- HVC Test of cure is not recommended in patients with *Chlamydia trachomatis* infection except in pregnancy; however, patients should be retested for possible repeat infection after 3 months or at their next medical visit.

Neisseria gonorrhoeae Infection

The incidence of *N. gonorrhoeae* infection has been increasing since 2013, with rates of infection increasing more rapidly among men than women. Persons aged 20 to 24 years are at highest risk. In addition to cervicitis, urethritis, pharyngitis, and rectal infection, disseminated gonococcal infection (presenting as arthritis-dermatitis syndrome) can occur (see MKSAP 18 Rheumatology). Infection can be asymptomatic, especially in women, so screening is recommended for women younger than 25 years and those 25 years and older with STI risk factors. The USPSTF does not recommend screening for men; the CDC recommends screening men at high risk, as for *C. trachomatis*.

H For screening and diagnosis, NAAT is preferred. Men and women can be screened using a first-catch urine sample; endocervical and urethral swabs may also be used. NAAT availability for samples from extragenital sites is limited, and physicians should determine what testing is available from their preferred laboratory. In patients with disseminated gonococcal infection (arthritis-dermatitis, endocarditis, or meningitis), all *N. gonorrhoeae* isolates should be tested for antimicrobial susceptibility. Patients with suspected disseminated gonococcal infection should have cultures performed on blood, joint fluid (if arthritis is present), purulent skin lesions (if present), and cerebrospinal fluid (if meningitis is suspected); however, culture yield is not high, so NAAT from all potential sites of exposure (genital, pharyngeal, rectal) should be obtained.

Treatment of *N. gonorrhoeae* is outlined in Table 32. Because of the increasing prevalence of antimicrobial resistance among *N. gonorrhoeae* isolates in the United States, cephalosporins are the only antimicrobial class recommended. Previously, the rationale for combination therapy was to treat concomitant *C. trachomatis* infection; the current rationale is based on increased efficacy of combination therapy. In the United States, *N. gonorrhoeae* isolates are more likely to be susceptible to azithromycin than doxycycline, and azithromycin can be given as a single dose. Doxycycline should only be used in the setting of macrolide allergy. In patients with an allergy precluding use of cephalosporins, oral gemifloxacin or parenteral gentamicin plus oral azithromycin is an option; however, the dose of azithromycin is higher, which is associated with a high incidence of gastrointestinal intolerance. H

Test of cure is only recommended 2 weeks after therapy when pharyngeal gonorrhea is treated with an alternate antibiotic regimen. Patients with infections caused by *N. gonorrhoeae* who do not respond to treatment should have repeat testing with NAAT and culture so that susceptibility data can be obtained; consultation with an expert in the management of these infections should be sought.

KEY POINTS

- Screening for *Neisseria gonorrhoeae* infection is recommended for women younger than 25 years and those 25 years and older with risk factors (new partner, more than one partner, a partner with an STI, or a partner who has concurrent partners).
- First-catch urine (or genital swab) sample nucleic acid amplification testing is the preferred screening and diagnostic method for *Neisseria gonorrhoeae* infection.
- Parenteral ceftriaxone with oral azithromycin is the preferred regimen for the treatment of *Neisseria gonorrhoeae* infection.
- Test of cure in patients with *Neisseria gonorrhoeae* infection is recommended 2 weeks after therapy only when pharyngeal gonorrhea is treated with an alternate antibiotic regimen. HVC

Clinical Syndromes

Cervicitis

Women with cervicitis may present with vaginal discharge and intermenstrual bleeding, but many are asymptomatic. The major diagnostic criteria are (1) visualization of mucopurulent discharge from the cervical os or on a swab obtained from the endocervical canal and (2) eliciting bleeding by passing a swab into the cervical os; cervicitis should be considered in women with either of these findings. *N. gonorrhoeae* and *C. trachomatis* are the most commonly isolated pathogens; however, many cases are enigmatic. The role of *Mycoplasma genitalium* is still unclear; herpes simplex virus is occasionally implicated. Noninfectious causes (for example, chemical irritation from douching) should be sought. Patients should be tested for *N. gonorrhoeae* and *C. trachomatis* with NAAT; evaluation for bacterial vaginosis and trichomoniasis should also be performed (see MKSAP 18 General Internal Medicine).

Pelvic Inflammatory Disease

Unrecognized pelvic inflammatory disease (PID) may result in long-term sequelae, including infertility, chronic pelvic pain, and ectopic pregnancy. Symptoms include lower abdominal pain, vaginal discharge, intermenstrual bleeding or bleeding after intercourse, and dyspareunia. Some women have fever and other signs of systemic toxicity, but this is uncommon.

The diagnostic accuracy of clinical examination is poor; however, because of the potential consequences of untreated infection, clinical findings with a high sensitivity for PID should be used. The presence of uterine tenderness, adnexal tenderness, or cervical motion tenderness is sufficient to make a clinical diagnosis of PID, especially if accompanied by mucopurulent cervical discharge.

PID is believed to be polymicrobial; however, testing only for *N. gonorrhoeae* and *C. trachomatis* is indicated. Most women can be managed in the ambulatory setting with oral antibiotics (see Table 32). Indications for hospitalization include inability to exclude a surgical emergency such as appendicitis, pregnancy, severe systemic toxicity, tubo-ovarian abscess, inability to tolerate oral antibiotics, and failure of initial outpatient management.

H Urethritis

Men with urethritis present with dysuria, urethral pruritus, and discharge. Mucopurulent discharge may be the only symptom and is clinically diagnostic. *N. gonorrhoeae*, *C. trachomatis*, and *M. genitalium* are common causes of urethritis; *Trichomonas* may also be causative. The role of other *Mycoplasma* and *Ureaplasma* species is uncertain at present. A first-catch urine sample should be tested for *N. gonorrhoeae* and *C. trachomatis* by NAAT for diagnosis and for public reporting purposes; FDA-approved tests for *M. genitalium* are not yet available. Microscopic examination of a urethral sample that reveals more than 2 leukocytes per high-powered field has a high positive predictive value for infectious urethritis, but the negative predictive value is poor. A positive leukocyte esterase test result or a microscopic examination with 10 or more leukocytes on a first-void urine specimen is also diagnostic for infectious urethritis. This testing is not required if mucoid, mucopurulent, or purulent urethral discharge is demonstrated on examination. H

Epididymitis

Men with epididymitis present with unilateral pain and swelling in the epididymis; the testes may also be inflamed (epididymo-orchitis). Testicular torsion must be excluded in men with symptoms of sudden onset. *N. gonorrhoeae* and *C. trachomatis* are likely causes in younger, sexually active men. Older men and men who practice insertive anal intercourse may be infected with enteric gram-negative organisms such as *Escherichia coli*. NAAT for STI pathogens should be performed on first-catch urine, and a urine culture should be obtained. See MKSAP 18 General Internal Medicine for further information.

Anorectal Infections

Patients who present with anorectal pain, rectal discharge, or tenesmus should be questioned regarding sexual practices. In addition to receptive anal intercourse, infection may occur in women as a result of autoinoculation from vaginal discharge. Causes include *C. trachomatis*, *N. gonorrhoeae*, syphilis, and herpes simplex virus (HSV). Infections caused by the lymphogranuloma venereum (LGV) serovars (L1, L2, or L3) of *C. trachomatis* had previously been rarely described in the United States, but they are increasingly reported as a cause of proctitis and proctocolitis, mainly among MSM.

Diagnostic evaluation should include NAAT for *C. trachomatis*, *N. gonorrhoeae*, and HSV as well as serologic testing for syphilis (dark-field examination should be performed if available). Additional molecular testing is required to identify LGV serovars of *C. trachomatis*, but it is not widely available commercially; LGV serovars of *C. trachomatis* will be detected by currently available NAATs.

KEY POINTS

- *Chlamydia trachomatis* and *Neisseria gonorrhoeae* are the primary causative organisms in cervicitis, pelvic inflammatory disease, urethritis, epididymitis, and anorectal infections, although other organisms may also be implicated.
- The two major diagnostic criteria of cervicitis are visualization of mucopurulent discharge from the cervical os or on a swab obtained from the endocervical canal or eliciting bleeding by passing a swab into the cervical os.
- The presence of uterine tenderness, adnexal tenderness, or cervical motion tenderness is sufficient to make a clinical diagnosis of pelvic inflammatory disease, especially if accompanied by mucopurulent cervical discharge.
- *Neisseria gonorrhoeae* and *Chlamydia trachomatis* are likely causes of epididymitis in younger, sexually active men; older men and men who practice insertive anal intercourse may be infected with enteric gram-negative organisms such as *Escherichia coli*.

Treatment

Treatment of the clinical syndromes discussed previously is outlined in Table 32. Symptomatic patients evaluated in urgent care centers or emergency departments and others who may not be able to return for follow-up should be treated empirically based on clinical syndrome. Diagnostic testing should still be obtained because STIs are reportable and test results will be informative if the infection fails to respond to empiric therapy.

Patients should abstain from sexual contact for 7 days after completion of therapy and until all sexual partners have been treated. Sexual partners in the previous 60 days, or the most recent partner if greater than 60 days, should be referred for evaluation and treatment. Although independent evaluation and testing of sexual partners is preferred, most states have provisions for providing empiric antibiotic therapy prescriptions to the patient for their partners (expedited partner therapy, or EPT).

KEY POINTS

- Diagnostic testing should be performed even if empiric therapy will be provided to patients unlikely to return for follow-up care, because *Neisseria gonorrhoeae* and *Chlamydia trachomatis* infections are reportable, and because test results will be informative if the infection fails to respond to therapy.
- Most states have provisions for providing empiric antibiotic therapy prescriptions for sexual partners (expedited partner therapy, or EPT).

Genital Ulcers

Herpes Simplex Virus

The epidemiology of HSV genital ulcer disease is changing; in some populations, such as young heterosexual women and MSM, HSV-1 is now a more common cause of symptomatic primary infection than HSV-2. Although the clinical manifestations of primary infection by HSV-1 and HSV-2 are indistinguishable, HSV-1 is less likely than HSV-2 to cause symptomatic recurrent ulcers and subclinical shedding. Differentiation between the two viral subtypes is important in counseling patients regarding the natural history of their infection.

Primary infection presents as multiple painful lesions that begin as erythematous papules, progress to vesicles, then ulcerate, crust, and eventually heal within 2 to 3 weeks (**Figure 12**). Primary infection is often accompanied by significant systemic symptoms. Tender inguinal lymphadenopathy may be present.

Although the clinical manifestations of primary infection are quite characteristic, the viral cause and HSV subtype should be confirmed. NAAT, such as polymerase chain reaction, for HSV-1 and HSV-2 is preferred; other methodologies are far less sensitive. Testing is performed by obtaining a swab from the ulcer base; if only vesicles are present, a vesicle must be unroofed to obtain cells from the ulcer base. The swab must be placed in viral transport medium, so the appropriate sample collection kit must be used. Type-specific serologic testing is not advised for the diagnosis of symptomatic ulcer disease because patients can be seropositive for HSV-1 or HSV-2 yet have genital ulcers from another cause. Potential roles for serologic testing include testing a sexual partner when evaluating the potential benefits of long-term suppressive therapy because a partner who is already infected would not be at risk for transmission. The CDC recommends considering HSV serologic testing in persons who present for STI evaluation, MSM, and persons with HIV infection. Serologic screening in the general population is not recommended.

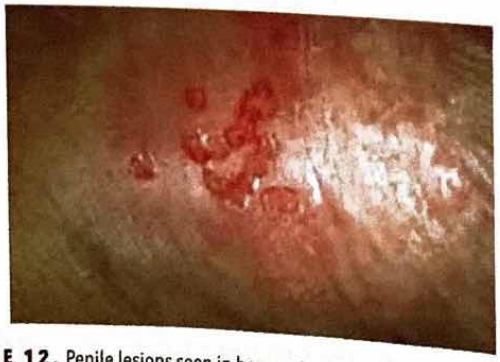

FIGURE 12. Penile lesions seen in herpes simplex virus (HSV) type 2. Patients with genital HSV infection initially have painful lesions that begin as vesicles and progress to ulcers on an erythematous base.

Antiviral therapy for primary infection has been shown to decrease time to resolution of symptoms, lesion healing, and viral shedding. Antiviral regimens appropriate for treatment of primary infection are outlined in **Table 33**.

Recurrent genital HSV infections are less severe, and symptom duration, time to lesion healing, and duration of viral shedding are reduced. Many patients will experience prodromal itching, burning, or tingling before ulcers appear. Atypical presentations such as fissures and excoriations may occur. Recurrent infection can be managed with either episodic self-start therapy (initiated within 24 hours of symptoms) or long-term suppressive therapy (see Table 33). Long-term suppressive therapy should be considered for persons with frequent recurrences and should be discussed with all patients because this strategy has been shown to decrease the risk of transmission to sexual partners. Laboratory monitoring is not required for patients undergoing long-term suppressive therapy; however, the continued need for therapy should be reviewed annually. Length of time since last recurrence and potential benefits of continued suppression in preventing

TABLE 33. Treatment of Herpes Simplex Virus Genital Infections

Clinical Syndrome	Recommended Regimen[a]
Primary infection[b]	Acyclovir, 400 mg three times daily, *or* acyclovir, 200 mg five times daily, *or* famciclovir, 250 mg three times daily, *or* valacyclovir, 1 g twice daily; all regimens for 7-10 days
Recurrent infection	Acyclovir, 400 mg three times daily for 5 days, *or* acyclovir, 800 mg twice daily for 5 days, *or* acyclovir, 800 mg three times daily for 2 days, *or* famciclovir, 125 mg twice daily for 5 days, *or* famciclovir, 1 g twice daily for 1 day, *or* famciclovir, 500 mg once followed by 250 mg twice daily for 2 days, *or* valacyclovir, 500 mg twice daily for 3 days, *or* valacyclovir, 1 g once daily for 5 days
Suppressive therapy	Acyclovir, 400 mg twice daily, *or* famciclovir, 250 mg twice daily, *or* valacyclovir, 500 mg daily[c], *or* valacyclovir, 1 g daily

[a]All regimens are given orally; topical preparations are not recommended for treatment of genital herpes simplex virus.

[b]Therapy can be extended if healing is incomplete after 10 days of treatment.

[c]The 500-mg dose of valacyclovir may be less effective than the 1-g dose in patients who have very frequent recurrences (≥10 episodes per year).

H CONT. transmission to sexual partners are factors that can inform the decision to stop suppressive therapy.

Patients should be counseled regarding the natural history of infection and informed that asymptomatic viral shedding is the most common source of HSV transmission to sexual partners. Condoms and abstinence from sexual activity when lesions are present can reduce the risk of transmission. Suppressive therapy to reduce risk of transmission should be discussed. Men and women should be counseled about the risks of neonatal HSV infection. Women should be advised to inform their obstetric provider and pediatrician of HSV infection in themselves or their sexual partner if they become pregnant. H

KEY POINTS

- Viral cause and herpes simplex virus subtype in primary infection should be confirmed by nucleic acid amplification testing, such as polymerase chain reaction, using a swab obtained from the ulcer base.
- The Centers for Disease Control and Prevention recommend considering herpes simplex virus serologic testing in persons who present for sexually transmitted infection evaluation, men who have sex with men, and persons with HIV infection; screening in the general population is not recommended.
- Long-term suppressive therapy of recurrent herpes simplex virus infection may be preferred over self-start episodic therapy because of decreased risk of transmission to sexual partners.

Syphilis

The incidence of primary and secondary syphilis has been increasing in the United States since 2000. The USPSTF recommends screening nonpregnant adolescents and adults at high risk of infection. Persons at risk include MSM and commercial sex workers and those with HIV infection, multiple sex partners, and previous syphilis. In 2015, the CDC issued a clinical advisory regarding the increasing incidence of ocular syphilis.

Primary syphilis presents as a painless genital ulcer (chancre) with a raised regular border that demonstrates firm induration on palpation (**Figure 13**). Several chancres may be present and may occur in the oral cavity. Regional lymphadenopathy may be present. The diagnosis of primary syphilis can be made on the basis of dark-field examination of material from a suspect lesion. Serologic test results may be negative in early primary infection. Even in the absence of treatment, lesions heal spontaneously in 3 to 6 weeks.

The most common manifestation of secondary syphilis is rash. Various morphologies are described; involvement of the palms and soles is characteristic. In intertriginous areas, papules may coalesce to form condyloma lata (plaque-like lesions). Mucous patches (superficial erosions on mucosal surfaces) may occur in the oral cavity and moist genital regions and are highly infectious. Prominent systemic symptoms and generalized lymphadenopathy are common. Uveitis and neurosyphilis (meningitis) can occur. Secondary syphilis manifestations can also resolve without treatment, followed by latent infection (a positive serologic test result without clinical manifestations). If latent infection is of less than 12 months' duration, it is termed early latent; if greater than 12 months' duration, it is late latent. Practically, these determinations can be made only if past serology results are available. Otherwise, patients are considered to have syphilis of unknown duration.

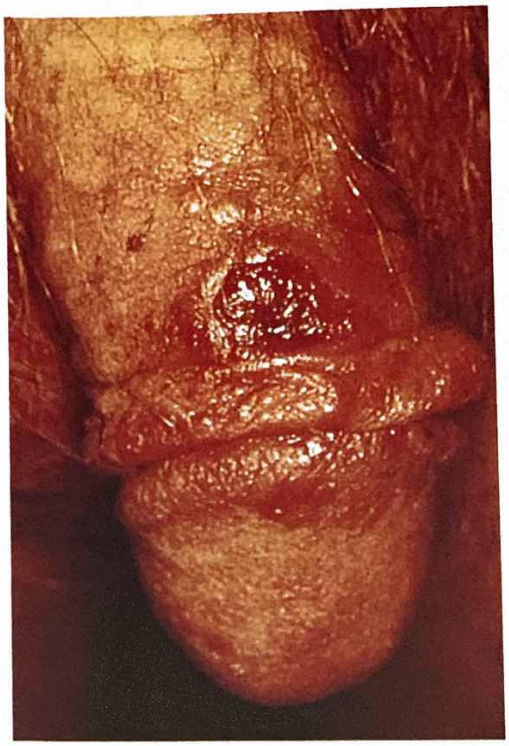

FIGURE 13. The primary ulcerative lesion (chancre) in patients with syphilis develops approximately 3 weeks after infection occurs, has a clean appearance with heaped-up borders, and is indurated and usually painless. It is often unrecognized.

Tertiary syphilis is rarely seen in the United States, although neurologic disease still occurs. Spinal fluid examination should be sought in any patient with unexplained neurologic symptoms and serologic evidence of syphilis as well as in those who do not demonstrate an appropriate serologic response to syphilis treatment.

Diagnosis of secondary and tertiary syphilis relies on serologic testing. Many laboratories use the "reverse" serologic testing strategy, starting with an automated enzyme immunoassay followed by a nonspecific test (rapid plasma reagin or Venereal Disease Research Lab test). Patients with a positive enzyme immunoassay result but negative rapid plasma reagin or Venereal Disease Research Lab test result should have a second specific treponemal antibody test to confirm the result. Those with a confirmed positive result and no history of syphilis treatment should be offered treatment for syphilis of unknown duration.

H CONT. Syphilis treatment is outlined in **Table 34**. Sexual partners of those with primary, secondary, or early latent syphilis exposed in the preceding 90 days should be treated regardless of serologic results. H

KEY POINTS

- Primary syphilis presents as a painless genital ulcer (chancre) with a raised regular border that demonstrates firm induration on palpation; lesions heal spontaneously in 3 to 6 weeks even without treatment.
- The most common manifestation of secondary syphilis is rash, with characteristic involvement of the palms and soles; in intertriginous areas, papules may coalesce to form condyloma lata (plaque-like lesions), and mucous patches (superficial erosions on mucosal surfaces) may occur in the oral cavity and moist genital regions and are highly infectious.
- Diagnosis of secondary and tertiary syphilis relies on serologic testing; patients with a positive enzyme immunoassay result and positive rapid plasma reagin or Venereal Disease Research Lab test result and no history of syphilis treatment should be offered treatment for syphilis of unknown duration.

Chancroid and Lymphogranuloma Venereum

With the exception of proctitis or proctocolitis caused by the LGV serovars of *C. trachomatis*, these two STIs are rarely seen in the United States. The clinical presentation and evaluation are outlined in **Table 35**, and treatment is outlined in **Table 36**.

Genital Warts

Genital warts have a variety of appearances, including papular or pedunculated lesions (**Figure 14**). Larger, verrucous, exophytic lesions can occur. Most are asymptomatic; however, large lesions may cause irritation or pain depending on their location. Nononcogenic types of human papillomavirus (HPV) are responsible for most lesions. Oncogenic subtypes less commonly cause genital warts. HPV infection can be diagnosed based on the presence of lesions with a consistent morphologic appearance. Specific testing for HPV is not recommended for diagnosis.

Warts will often resolve without therapy, but treatment is indicated for symptomatic warts or if the cosmetic appearance of the warts is causing psychological distress. Patients should be counseled that successful treatment may not eliminate the risk of transmission. Therapy includes patient-applied

TABLE 34. Treatment of Syphilis

Stage	Recommended Regimen[a]	Alternate Regimen for Penicillin-Allergic Patients
Primary and secondary	Benzathine penicillin G, 2.4 million units IM single dose	Doxycycline, 100 mg PO twice daily, *or* tetracycline, 500 mg PO four times daily, for 14 days
Early latent	Benzathine penicillin G, 2.4 million units IM single dose	Doxycycline, 100 mg PO twice daily, *or* tetracycline, 500 mg PO four times daily, for 14 days
Late latent or syphilis of unknown duration	Benzathine penicillin G, 2.4 million units IM at 1-week intervals for 3 doses	Doxycycline, 100 mg PO twice daily, *or* tetracycline, 500 mg PO four times daily, for 28 days
Neurosyphilis	Aqueous crystalline penicillin G, 18-24 million units daily given as 3-4 million units IV every 4 hours or by continuous infusion for 10-14 days, *or* procaine penicillin, 2.4 million units IM daily, plus probenecid, 500 mg PO four times daily, both for 10-14 days	Ceftriaxone, 2 g IM or IV daily for 10-14 days[b]

IM = intramuscularly; IV = intravenously; PO = orally.

[a]Penicillin is the only effective antimicrobial agent for treatment of syphilis at any stage in pregnancy; therefore, pregnant penicillin-allergic patients should be desensitized and treated with the appropriate penicillin regimen as outlined above.

[b]Limited data are available to support the use of this alternate regimen, and the possibility of cross-reaction in penicillin-allergic patients must be considered. In patients who cannot take ceftriaxone, penicillin desensitization is recommended.

TABLE 35. Clinical Presentation and Diagnosis of Chancroid and Lymphogranuloma Venereum

Clinical Entity	Causative Agent	Presentation	Diagnosis
Chancroid	*Haemophilus ducreyi*	Painful genital ulcer; tender inguinal lymph nodes, which often suppurate	Culture is difficult; consider diagnosis if painful ulcer with tender and suppurative regional lymphadenopathy, no evidence of syphilis by dark-field examination or serology, and negative HSV PCR or HSV culture
LGV	L1, L2, and L3 serovars of *Chlamydia trachomatis*	Painless genital papule or ulcer with unilateral tender inguinal lymphadenopathy	NAAT for *C. trachomatis*; does not distinguish the serovars, so diagnosis is made based on clinical and epidemiologic findings

HSV = herpes simplex virus; LGV = lymphogranuloma venereum; NAAT = nucleic acid amplification test; PCR = polymerase chain reaction.

TABLE 36. Treatment of Chancroid and Lymphogranuloma Venereum

Clinical Entity	Recommended Regimen
Chancroid	Azithromycin, 1 g PO single dose, *or* ceftriaxone, 250 mg IM single dose, *or* ciprofloxacin, 500 mg PO twice daily for 3 days, *or* erythromycin base, 500 mg PO three times daily for 7 days
Lymphogranuloma venereum	Doxycycline[a], 100 mg PO twice daily for 21 days (preferred), *or* erythromycin base, 500 mg PO four times daily for 21 days (alternate)

IM = intramuscularly; PO = orally.

[a]Doxycyline should be avoided or used with caution in pregnant patients.

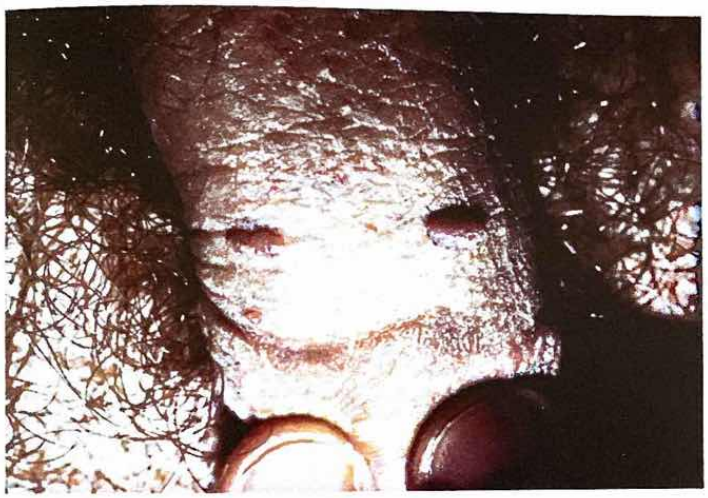

FIGURE 14. Genital warts caused by human papillomavirus infection are typically flesh colored and exophytic; pedunculated lesions often occur.

or physician-administered modalities. Patient-applied therapies include imiquimod, podofilox, and sinecatechins; provider-administered therapies include trichloroacetic acid or bichloroacetic acid, cryotherapy with liquid nitrogen or cryoprobe, or surgical removal. The modality chosen depends on size, number, and location of warts; patient preference; and provider experience. No evidence indicates superiority of any of the modalities recommended. Ulcerated or pigmented warts and those that fail to respond to or worsen after therapy should be biopsied to exclude a cancerous lesion.

KEY POINT

- Nononcogenic types of human papillomavirus are responsible for most genital warts, which often resolve without therapy.

Osteomyelitis

Osteomyelitis occurs as a result of hematogenous dissemination or contiguous spread of bacteria. Hematogenous osteomyelitis in adults most commonly affects vertebral bodies, although involvement of other sites has been described, particularly in persons who inject drugs. Contiguous-spread osteomyelitis may arise from direct contamination (fracture, joint replacement, orthopedic implant), wounds (pressure sores, diabetic foot ulcers), or adjacent soft tissue infection. Population-based studies suggest that the incidence of osteomyelitis among adults is increasing in the United States, most likely because of the increasing prevalence of diabetes mellitus. Osteomyelitis can be difficult to diagnose, can cause indolent infections that persist for prolonged periods, and requires long-term antibiotic treatment; thus, the economic impact of this infection is substantial.

Clinical Manifestations

Osteomyelitis frequently presents as subacute or chronic pain over the affected region of bone. If osteomyelitis has resulted from direct contamination of a wound, the wound may fail to heal or may reopen after healing. Spontaneously opening wounds accompanied by drainage (sinus tracts) are a late manifestation of infection. Underlying osteomyelitis should be considered when chronic wounds, such as pressure ulcers, do not respond to appropriate therapy. Fever and other systemic manifestations of infection are not common but are more likely in patients with acute hematogenously disseminated infection. Clinical findings in patients with diabetes-associated foot ulcer osteomyelitis and vertebral osteomyelitis are discussed separately.

KEY POINTS

- Osteomyelitis frequently presents as subacute to chronic pain over the affected region of bone; fever and other systemic manifestations of infection are uncommon.
- Underlying osteomyelitis should be considered when chronic wounds, such as pressure ulcers, do not respond to appropriate therapy.

Diagnosis

Laboratory and Imaging Studies

Laboratory studies are nondiagnostic for osteomyelitis. Elevated inflammatory markers, such as erythrocyte sedimentation rate or C-reactive protein level, increase the pretest probability of infection and can be useful in monitoring therapeutic response; normal inflammatory markers alone are insufficient to exclude the diagnosis. Except in acute hematogenous osteomyelitis, leukocytosis is uncommon; in chronic osteomyelitis, anemia may be present. Blood culture results are rarely positive, except in patients with hematogenous osteomyelitis (such as vertebral osteomyelitis). Blood cultures should be obtained when hematogenous osteomyelitis is suspected or in patients with systemic manifestations of sepsis.

Plain radiography is not adequately sensitive to exclude a diagnosis of osteomyelitis, but it is recommended during