COURSE #98721 — 5 CONTACT HOURS/CREDITS Release Date: 05/01/23 Expiration Date: 04/30/26

Bacterial Sexually Transmitted Infections

HOW TO RECEIVE CREDIT

- Read the enclosed course.
- Complete the questions at the end of the course.
- Return your completed Evaluation to NetCE by mail or fax, or complete online at www.NetCE.com. (If you are a physician or Florida nurse, please return the included Answer Sheet/Evaluation.) Your postmark or facsimile date will be used as your completion date.
- Receive your Certificate(s) of Completion by mail, fax, or email.

Faculty

Mark Rose, BS, MA, LP, is a licensed psychologist in the State of Minnesota with a private consulting practice and a medical research analyst with a biomedical communications firm. Earlier healthcare technology assessment work led to medical device and pharmaceutical sector experience in new product development involving cancer ablative devices and pain therapeutics. Along with substantial experience in addiction research, Mr. Rose has contributed to the authorship of numerous papers on CNS, oncology, and other medical disorders. He is the lead author of papers published in peer-reviewed addiction, psychiatry, and pain medicine journals and has written books on prescription opioids and alcoholism published by the Hazelden Foundation. He also serves as an Expert Advisor and Expert Witness to law firms that represent disability claimants or criminal defendants on cases related to chronic pain, psychiatric/substance use disorders, and acute pharmacologic/toxicologic effects. Mr. Rose is on the Board of Directors of the Minneapolis-based International Institute of Anti-Aging Medicine and is a member of several professional organizations.

Faculty Disclosure

Contributing faculty, Mark Rose, BS, MA, LP, has disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

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The division planners and director have disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

Audience

This course is designed for physicians, physician assistants, nurses, pharmacists, and allied health professionals involved in the care of patients at risk for or with bacterial sexually transmitted infections.

Accreditations & Approvals

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INTERPROFESSIONAL CONTINUING EDUCATION

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A complete Works Cited list begins on page 35.

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NetCE designates this continuing education activity for 4 pharmacotherapeutic/pharmacology contact hours.

AACN Synergy CERP Category A.

NetCE designates this activity for 5 hours ACPE credit(s). ACPE Universal Activity Numbers: JA4008164-0000-23-008-H01-P and JA4008164-0000-23-008-H01-T.

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Special Approvals

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About the Sponsor

The purpose of NetCE is to provide challenging curricula to assist healthcare professionals to raise their levels of expertise while fulfilling their continuing education requirements, thereby improving the quality of healthcare.

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Disclosure Statement

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Course Objective

The purpose of this course is to enhance clinician knowledge regarding the most common bacterial sexually transmitted infections in order to ensure that diagnosis and treatment is initiated early, when transmission risk and sequelae can be minimized.

Learning Objectives

Upon completion of this course, you should be able to:

1. Describe the epidemiology and impact of bacterial sexually transmitted infections (STIs).
2. Discuss best practice screening guidelines for bacterial STIs.
3. Describe the approach to diagnosis, prevention, and management of chlamydia.
4. Review clinical recommendations for the diagnosis and management of gonorrhea infection.
5. Analyze the appropriate approach to syphilis diagnosis, prevention, and treatment.
6. Discuss clinical issues related to the transmission, detection, and management of other bacterial STIs, including rare and emerging infections.
7. Assess management issues that may arise when caring for patients with bacterial STIs, including issues related to antimicrobial resistance.

Pharmacy Technician Learning Objectives

Upon completion of this course, you should be able to:

1. Outline the epidemiology of and screening for bacterial STIs.
2. Discuss recommendations for the assessment and treatment of bacterial STIs.

EVIDENCE-BASED PRACTICE RECOMMENDATION

Sections marked with this symbol include evidence-based practice recommendations. The level of evidence and/or strength of recommendation, as provided by the evidence-based source, are also included so you may determine the validity or relevance of the information. These sections may be used in conjunction with the course material for better application to your daily practice.

INTRODUCTION

Sexually transmitted infections, or STIs, are clinical syndromes caused by pathogens acquired and transmitted through sexual activity. STI prevalence is increasing throughout the world, a major clinical and public health challenge rooted in the complexities of social engagement and sexual behavior. The World Health Organization (WHO) and the Centers for Disease Control and Prevention (CDC) conduct surveillance of STIs and provide updated clinical guidance on prevention, diagnosis, and management of STI [1; 3; 4]. This course will address the predominant bacterial STIs in the United States, the major forms of which are increasing at alarming rates.

CDC surveillance data show that from 2016 to 2020, increases were observed in syphilis and gonorrhea [1]. More than 20 million new STI cases occurred, with people 15 to 24 years of age accounting for around 50% of new cases. The annual estimated direct medical cost of STIs is $16 billion [2]. Most costs are attributable to HIV ($13.7 billion), chlamydia ($691 million), gonorrhea ($271 million), and herpes simplex virus-2 (HSV-2) ($91 million) [1].

Following a transient decrease in case reports during the first six months of the COVID-19 pandemic, preliminary CDC data for 2021 show that reported cases of chlamydia, gonorrhea, and syphilis (totaling 2.5 million) continued to increase, with no signs of slowing. From 2020 to 2021, the one-year increase in reported cases was 3.1% for chlamydia, 2.8% for gonorrhea, and 25.7% for primary and secondary syphilis [90].

By 2010, rates of gonorrhea had reached historic lows, syphilis was close to elimination, and advances in diagnostic tests and screening had led to increased detection and treatment of chlamydial infections. This progress has reversed. The number of reported syphilis cases is climbing after being largely in decline since 1941. Gonorrhea rates are now increasing, and treatment options are limited as a result of antimicrobial resistance [1; 4]. These increases are unlikely to be due to better screening or referral.

Despite the availability of comprehensive guidelines for clinical testing and treatment of STIs, studies have shown that compliance is poor; in one study, fewer than one-third of STI cases managed in an emergency department received recommended antimicrobial treatment, and compliance with recommendations for directed history, diagnostic testing, and counseling ranged from 14% to 79% [60]. In addition, there are patient and societal barriers to timely treatment and effective preventive measures; these include incarceration, poverty, stigma, and homophobia. The resurgence in STIs has been attributed to a deteriorating public health infrastructure and lack of access to health care. In 2012, 52% of state and local STI programs experienced budget cuts, and 21 local health department STI clinics closed that year alone. Fewer clinics create greater barriers to STI testing and treatment, exposing hidden, fragile populations in need that are not obtaining health care and preventive services [1; 2].

STI prevention and control is based on five primary strategies, implemented according to the latest recommendations [4; 35]:

- Accurate risk assessment, education and counseling of patients at risk of STI to avoid high-risk behaviors and use prevention services
- Pre-exposure vaccination for vaccine-preventable STIs
- Identification of persons with asymptomatic infection or STI symptoms
- Diagnosis, treatment, counseling, and follow-up of patients with infections
- Evaluation, treatment, and counseling for sex partners of patients with STIs

EPIDEMIOLOGY

HISTORICAL TRENDS

Epidemiologic statistics are obtained and reported to monitor the extent of new infections, including subgroups with vulnerability, and to track changes over time in new infections. The total number of persons with newly diagnosed infection (cases) is valuable for understanding the magnitude of impact at a given point in time, while comparisons over time are more accurate using incidence rates (new cases per 100,000 population) [1].

Chlamydia

Records of new chlamydia cases began in 1984. Since then, case rates gradually increased, with 251.4 per 100,000 population reported in 2000, 405.3 per 100,000 population in 2009, and a peak of 539.9 per 100,000 population in 2018 [1]. Since 2018, the rates have decreased. In 2020, the rate was 481.3 cases per 100,000 population, a decrease of 13% compared with the rate in 2019 [1]. Chlamydial infection is diagnosed more than twice as often in women than men, and rates are highest among adolescents and young adults.

Gonorrhea

Population rates of gonorrhea rose from 1941 levels (146.7 per 100,000 population) to peak in 1976 (460.6 per 100,000 population), declined to an all-time low in 2009 (98.1 per 100,000 population), but are rising again as of 2020 (206.5 per 100,000 population) [1]. In 2020, the reported case rate (per 100,000) of gonorrhea was higher among men (250) than among women (150). The higher rate of infection among men compared to women is likely because cases are readily identified not only in men who have sex with women but also in men who have sex with men (MSM) [1].

Syphilis

Population rates of syphilis infection were the highest recorded in 1943 (447.0 per 100,000 population), slowly declining until 1978 (29.2 per 100,000 population), and then doubling by 1990 (54.3 per 100,000 population). Rates then began declining again until 2005 (11.2 per 100,000 population), following which case rates have risen every year, reaching 40.6 per 100,000 in 2020, a 6.8% increase over that for 2019 [1]. Preliminary data for 2021 shows that total reported cases of syphilis increased from 133,955 in 2020, to 171,074 in 2021, a 27.7% increase [90]. Primary and secondary syphilis, the most infectious stages, increased from 41,665 to 52,354. Young MSM are disproportionately impacted, accounting for the majority (53%) of all male syphilis cases in 2020.

Chancroid

Chancroid rates rose from 1941 levels (2.5 per 100,000 population) to peak in 1947 (6.7 per 100,000 population), declined until 1978 (0.2 per 100,000 population) and rose again until 1987 (2.1 per 100,000 population), but declined again to remain at historic lows in 2020 (<0.1 per 100,000 population) [1].

CURRENT TRENDS

Notifiable diseases are specified infectious and non-infectious conditions for which regular, frequent, and timely information regarding individual cases is considered necessary for prevention and control of the disease. Public health department reporting is mandated for all new cases of notifiable disease [5]. The list of notifiable diseases, including STIs, is reviewed annually for revision as needed. Notifiable STIs for 2020 include [6]:

- Human immunodeficiency virus (HIV)
- Chlamydia
- Gonorrhea
- Syphilis (all stages)
- Hepatitis A, B, and C
- Chancroid
- Zika virus

BACTERIAL STI STATISTICS AND TRENDS, 2021			
Characteristic/Population	**Chlamydia**	**Gonorrhea**	**Syphilis[a]**
Total Cases (and Rate per 100,000 Population)			
2009	1,244,180 (405.3)	301,174 (98.1)	13,997 (4.6)
2014	1,441,789 (452.2)	350,062 (109.8)	19,999 (6.3)
2021	1,644,416 (481.3)	710,151 (206.5)	53,767 (16.2)
Increase between 2009 and 2021	32.2%	135.8%	284.1%
Rate By Age (per 100,000 Population)			
15 to 19 years of age	1,743.1	472.6	9.8
20 to 24 years of age	2,724.0	860.5	35.8
25 to 29 years of age	1,378.0	661.5	45.7
30 to 34 years of age	729.0	473.5	43.7
Prevalence By Sex[b]			
Male	35.7%	57.8%	76.9%
Female	64.0%	42.0%	22.8%
Rate By Race/Ethnicity (per 100,000 Population)			
Black	1,081.9	652.9	41.9
American Indian/Alaska Native	650.6	370.9	46.7
Native Hawaiians/Other Pacific Islanders	563.2	204.9	33.9
Hispanic	349.4	137.0	17.2
White	184.9	78.9	9.1
Asian	95.7	37.8	4.8
Multi-race	280.7	162.2	19.4

[a]Primary and secondary cases of syphilis only.
[b]Percentages may not total 100% due to cases with unknown or nonbinary sex.

Source: [1; 90] *Table 1*

Chlamydia, gonorrhea, and syphilis are nationally notifiable STIs for which there are federally funded control programs. These STIs have the most extensive data collected. STI epidemiology publications use figures from estimates or from reported cases (***Table 1***). Based on these data, Black Americans had the highest rates among racial/ethnic groups, followed by American Indians and Hispanic Americans. Asian Americans had lower rates than White Americans [1].

Syphilis is only infectious and contagious during the primary and secondary stages; thus, the trending yearly increased incidence is a major public health concern. Although they remain disproportionately affected (representing 53% of male cases), increases among MSM have slowed in recent years and during 2019–2020, the number of cases of primary and secondary syphilis among MSM decreased 2.2% [1]. Rates of primary and secondary syphilis are lower among women, but rates have increased 21% during 2019–2020 and 147% during 2016–2020, suggesting that the heterosexual syphilis epidemic continues to rapidly increase in the United States [1].

GENERAL STI ASSESSMENT AND PREVENTION COUNSELING

The prevalence of STIs can be lowered by a consistent, concerted clinical and public health effort to prevent infection and control spread. Strategies for prevention include risk assessment, education, and counseling; limiting the number of sexual partners; and abstinence or use of condoms and barriers to sexual transmission. The importance of abstaining from sexual activity while undergoing treatment should be emphasized to individuals with a confirmed STI. Effective control measures require identification and treatment of asymptomatic sexual partners of known cases and symptomatic individuals who may not seek health care. The CDC encourages clinicians to promote prevention with patient-centered education that focuses on risk reduction measures directed at the individual patient's personal risk [4]. Obtaining a thorough sexual history is essential to primary prevention and control of spread.

SEXUAL HISTORY TAKING IN PATIENT INTERVIEWS

The "Five Ps" approach elicits sexual history information related to five key areas of interest: partners, practices, prevention of pregnancy, protection against STIs, and past history of STI [4].

Partners

- "Do you have sex with men, women, or both?"
- "In the past two months, how many partners have you had sex with?"
- "In the past 12 months, how many partners have you had sex with?"
- "Is it possible that any of your sex partners in the past 12 months had sex with someone else while they were still in a sexual relationship with you?"

Practices

- "To understand your risks for STIs, I need to understand the kind of sex you have had recently."
- "Have you had oral sex, meaning 'mouth on penis/vagina' sex?"
- "Have you had vaginal sex, meaning 'penis in vagina' sex?"
- "Have you had anal sex, meaning 'penis in rectum/anus' sex?"
- If yes to any of the questions above, "Do you use condoms: never, sometimes, or always?"
  - If "never:" "Why don't you use condoms?"
  - If "sometimes:" "In what situations (or with whom) do you use condoms?"

Prevention of Pregnancy

- "What are you doing to prevent pregnancy?"

Protection against STIs

- "What do you do to protect yourself from STIs and HIV?"

Past History of STIs

- "Have you ever had an STI?"
- "Have any of your partners had an STI?"

Practical strategies for risk assessment and counseling are provided in the CDC treatment guidelines document [4]. Health providers should use simple, direct language when asking these questions, taking care to exhibit respect, compassion, and a nonjudgmental attitude. Organizations such as the National Network of STI/HIV Prevention Training Centers, a CDC-funded group, can help providers enhance skills in counseling individuals about prevention. Resources can be found on the organization's website at https://www.cdc.gov/std/treatment/resources.htm.

STI BEHAVIORAL COUNSELING

Intensive behavioral counseling interventions to prevent STIs are recommended for all sexually active adolescents and adults at increased risk for STIs.

Risk Assessment

All sexually active adolescents are considered at increased risk for STIs and should be counseled. Other at-risk groups include adults with current or past-year STIs with multiple sex partners or who use condoms inconsistently. As noted, Black Americans have the highest STI prevalence of any racial/ethnic group, and STI prevalence is higher in American Indians, Alaska Natives, and Latino/as than in white populations. Increased STI prevalence rates are also found in MSM, persons with low incomes living in urban settings, current or former inmates, military recruits, persons who exchange sex for money or drugs, persons with mental illness or a disability, current or former injecting drug users, persons with sexual abuse history, and patients of public STI clinics [7].

Behavioral Counseling Interventions

Behavioral counseling interventions can reduce the risk of acquiring an STI. Interventions ranging in intensity from 30 minutes to more than two hours of contact time are beneficial; evidence of benefit increases with intervention intensity [7]. Interventions can be delivered by primary care clinicians or through referral to trained behavioral counselors. Successful interventions provide basic information on STIs and STI transmission; assess patient risk for transmission; and provide pertinent skills training, such as condom use, communication about safe sex, problem solving, and goal setting. Many successful interventions aim to increase motivation or commitment to safe sex practices [7].

As a result of the evolving racial and immigration demographics in the United States, interaction with patients for whom English is not a native language is inevitable. Because communication with patients and families is considered an essential aspect of care, it is each practitioner's responsibility to ensure that information regarding goals and potential outcomes are explained in such a way that allows for patient understanding. When there is an obvious disconnect in the communication process between the practitioner and patient due to the patient's lack of proficiency in the English language, an interpreter is required.

BARRIER AND NONBARRIER APPROACHES TO PREVENT OR REDUCE STI TRANSMISSION AND INFECTION

EXTERNAL CONDOMS

When used consistently and correctly, external latex condoms (also referred to as male latex condoms) are highly effective in the prevention of chlamydia and gonorrhea and reducing risks for syphilis and chancroid when the infected area or site of potential exposure is covered [8; 9; 10]. By limiting lower genital tract infections, condoms may reduce the risk of later pelvic inflammatory disease (PID) in women [4; 11].

As U.S. Food and Drug Administration (FDA)-regulated medical devices, condoms are subject to quality-control testing. Each latex condom manufactured in the United States is tested electronically for holes before packaging. The rate of condom breakage during sexual intercourse and withdrawal is approximately 2 per 100 condoms used, with slightly higher rates during anal intercourse [12; 13]. Condom failure to protect against STI or unintended pregnancy is usually caused by inconsistent or incorrect use, instead of condom breakage [14]. Latex condoms should not be used beyond their expiration date or more than five years after the manufacturing date, and users should check the expiration or manufacture date on the packaging before use [4]. In 2022, the FDA cleared the first natural rubber latex condom designed specifically to be used in anal intercourse [101].

External condoms made of materials other than latex fall in two general categories: synthetic and natural membrane condoms. Polyurethane and other synthetic condoms provide protection against STIs and pregnancy comparable to latex condoms and are used mainly as latex condom substitutes by persons with latex allergy. These condoms are more resistant to deterioration and are compatible with oil-based or water-based lubricants. The preventive efficacy of other synthetic external condoms is not well studied, and the FDA restricts their use to persons with latex sensitivity or allergy [10; 15].

Natural membrane condoms (termed "natural skin" or "lambskin") are made from lamb cecum. The pores, no greater than 1,500 nm in diameter, block passage of sperm but are more than 10 times the diameter of HIV and more than 25 times that of HBV. Therefore, sexual transmission of hepatitis B, herpes simplex, and HIV organisms can occur with natural membrane condoms; it is believed that bacterial transmission is also possible. These condoms are recommended for preventing pregnancy but not STIs/HIV [15; 16; 17].

Providers should communicate guidance to patients to ensure correct external condom use [4]. Consistent, correct use is essential to prevent STIs/HIV infection, and a new condom should be used with each oral, vaginal, and anal sex act. It is important to carefully handle condoms to avoid damage from fingernails, teeth, or other sharp objects. Condoms should be put on after the penis is erect and before genital, oral, or anal contact. To prevent the condom from slipping off, the condom should be held firmly against the base of the penis during withdrawal, which should occur while the penis is still erect.

Adequate lubrication during vaginal and anal sex will help prevent condom breakage. With latex condoms, patients should be advised to use only water-based lubricants such as K-Y Jelly, Astroglide, Aqua Lube, or glycerin. Oil-based lubricants (e.g., petroleum jelly, shortening, mineral oil, massage oils, body lotions, cooking oil) weaken latex and should not be used, but are compatible with synthetic condoms.

INTERNAL CONDOMS

Several condoms are available for internal use (also referred to as female condoms), including the FC2 Female Condom, Reddy condom, Cupid female condom, and Woman's condom. Internal condoms can protect from acquisition and transmission of STIs, but data are limited compared with external condoms. Internal condoms are more expensive but offer the advantage of being a female-controlled STI/HIV prevention method, and newer versions may have greater acceptability to both men and women. While internal condoms have been used during receptive anal intercourse, the efficacy is unknown [18; 19].

INEFFECTIVE METHODS

Cervical Diaphragms

Uncontrolled studies found that diaphragms protected against cervical gonorrhea, chlamydia, and trichomoniasis, but controlled studies found that compared with external condoms, diaphragms plus lubricant did not reduce rates of chlamydia or gonorrhea [20]. Diaphragms should not be solely relied on for protection against HIV/STIs [21; 22].

Non-Barrier Contraception

Contraceptive methods that are not mechanical barriers provide no protection against HIV or other STIs. Sexually active patients who use hormonal contraception, nonhormonal intrauterine devices, or have been surgically sterilized or undergone a hysterectomy should be advised to use condoms to reduce risks for STIs [15].

Genital Hygiene

Vaginal washing and douching after sexual exposure are ineffective and may increase the risk for bacterial vaginosis, some STIs, and HIV infection [4; 23].

SCREENING

GENERAL SCREENING RECOMMENDATIONS

STI screening is an essential component of overall efforts to reduce STI acquisition and transmission and of individual risk assessment, but it is underutilized. STIs themselves are biologic markers of risk for additional STIs, particularly for HIV in some patients [24]. As such, all persons seeking evaluation or treatment for a suspected STI should be screened for HIV and other STIs. The CDC has established guidelines for screening for bacterial STIs in specific populations (***Table 2***). The decision to recommend specific STI screening is determined by community prevalence and by individual demographics and STI risk factors. Clinicians should provide patients with information regarding all STIs for which they are being tested and of tests available for common STIs (such as genital herpes and HPV) that are not being provided [24].

BACTERIAL STI SCREENING RECOMMENDATIONS						
Infection	**Population Screened**					
	Women	**Pregnant Women**	**Men**	**MSM**	**Persons with HIV**	**Transgender and Gender-Diverse Persons**
Chlamydia	All younger than 25 years of age if sexually active 25 years of age or older if sexually active and at risk	All younger than 25 years of age All 25 years of age or older if at risk Retest in third trimester if younger than 25 years of age or at risk Test-of-cure 3 to 4 weeks after treatment and retest within 3 months	Consider for young men in high-risk settings	At least yearly if sexually active, at sites of contact (urethra, rectum, pharynx)[a] Every 3 to 6 months if at risk	If sexually active, screen at first HIV testing and then at least yearly More frequent screening based on risk behaviors and local prevalence	Recommendations should be adapted based on anatomy (e.g., recommendations for women may be applied to any person with a cervix). Consider screening at the rectal site based on risk behaviors
Gonorrhea	All younger than 25 years of age if sexually active 25 years of age or older if sexually active and at risk Retest 3 months post-treatment	All younger than 25 years of age All 25 years of age or older if at risk Retest 3 months post-treatment	—	At least yearly if sexually active, at sites of sexual contact[a] Every 3 to 6 months if at risk	If sexually active, screen at first HIV testing and then at least yearly More frequent screening based on risk behaviors and local prevalence	Recommendations should be adapted based on anatomy. Consider screening at the pharyngeal or rectal site based on risk behaviors
Syphilis	Pharyngeal and/or rectal screening based on risk behaviors	All women at first prenatal visit Retest early in third trimester and at delivery if high risk	—	At least yearly if sexually active Every 3 to 6 months if at risk	If sexually active, screen at first HIV testing and then at least yearly More frequent screening based on risk behaviors and local prevalence	Consider screening at least annually based on risk behaviors
[a]Regardless of condom use						
Source: [25; 26]						*Table 2*

Retesting several months after diagnosis of some STIs is required to detect recurrent or treatment-nonresponsive infection. All persons testing positive for chlamydia or gonorrhea should be rescreened three months after treatment. All persons with a syphilis diagnosis should undergo follow-up serologic syphilis testing based on current practice recommendations [25].

Risk factors also determine STI screening frequency. Sexually active MSM (regardless of HIV status) should be screened for oral gonorrhea and for rectal gonorrhea and chlamydia at least annually (depending on reported sex practices) and every three to six months when risk behaviors persist or if they or their sexual partners have multiple partners [24]. STI risk factors that help determine screening frequency for any given person include [4]:

- Presentation in high-risk settings: Adolescent or STI clinics, correctional facilities
- At-risk women: A new sex partner, more than one sex partner, a sex partner with concurrent partners or an STI
- High-risk women: Multiple sex partners, exchanges sex for money or drugs, illicit drug use, history of STI
- Gonorrhea, in women: Same as high-risk, plus inconsistent condom use and not in mutually monogamous relationships
- Chlamydia, in women: Same as high-risk, plus previous chlamydia infections even if treated and/or living in a detention facility
- Men: Multiple sex partners
- High-risk MSM: HIV infection and persistent risk behaviors, sexual partner has multiple partners

Many STIs are screened because they are often asymptomatic during initial infection and likely to be unknowingly transmitted, and their detection is essential to avoid serious complications from untreated infection.

CHLAMYDIA SCREENING

Most persons infected with *Chlamydia* lack symptoms that would prompt their seeking of medical care. Screening is necessary to identify and treat this infection, because most persons are unaware of their *Chlamydia trachomatis* infection, and untreated infection can have serious consequences. Up to 30% of untreated women develop PID, associated with infertility, debilitating chronic pelvic pain, and life-threatening tubal pregnancy. Chlamydial infection during pregnancy can lead to infant conjunctivitis and pneumonia and maternal postpartum endometriosis. Rectal chlamydia infection may lead to proctocolitis. In men, urethritis is the most common illness resulting from C. *trachomatis* infection, which progresses to epididymitis in a subset of patients [27].

GONORRHEA SCREENING

Gonococcal infections tend to cause stronger inflammatory responses than C. *trachomatis*, and while urethral infections often cause discharge and pain with urination, cervical, pharyngeal, and rectal infections are frequently asymptomatic. Untreated gonococcal infection is a major cause of PID in women; disseminated gonococcal infection can result in localized septic arthritis, endocarditis, and meningitis. Furthermore, gonococcal infection increases the risk of HIV. For these reasons, screening for gonorrhea is recommended in specific populations [28].

The U.S. Preventive Services Task Force recommends screening for chlamydia and gonorrhea in sexually active women 24 years of age and younger and in women 25 years of age and older who are at increased risk for infection.

(https://jamanetwork.com/journals/jama/fullarticle/2784136. Last accessed April 24, 2023.)

Level of Evidence: B (High certainty that the net benefit is moderate or moderate certainty that the net benefit is moderate to substantial)

DIAGNOSTIC TESTING

Nucleic acid amplification tests (NAATs) detect the DNA genetic material of many STIs in specimens obtained by endocervical, vaginal, or urethral swab, first-catch urine samples, or oropharyngeal and rectal swab [29; 30]. Culture tests grow bacteria from a specimen to detect STIs; they may also be used to detect inflammatory markers in urethral or genital secretions. Examples include Gram stain and methylene blue/gentian violet stain. Direct detection of bacteria is performed by examining a scraping or exudate specimen using a dark-field microscope, or by other methods.

In 2021, the FDA expanded approval of an NAAT to include use in point-of-care settings, including physician offices, health clinics, urgent care settings, and outpatient facilities [147]. The test, which uses female vaginal swabs and male urine specimens, can detect the presence of the bacteria *Chlamydia trachomatis* and *Neisseria gonorrhoeae* and provides results in about 30 minutes, allowing for earlier initiation of therapy for confirmed infection.

PARTNER SERVICES

For decades, partner services programs have been a foundation of state and local public health department STI control. Standard STI partner services identify, locate, and notify sex partners of infected persons to offer referral to evaluation, treatment, and care. The objective of partner services programs is to interrupt the chain of STI transmission at a level sufficient to reduce morbidity, achieved by identifying and treating undiagnosed STIs. Partner services intervene in disease progression (including incubating disease) and prevent serious sequelae, such as congenital syphilis. Partner services also contribute to understanding STI epidemiology by collecting data [31].

The types of public health partner services, and specific STIs for which services are offered, vary by agency and geographic burden of STIs. Most health departments provide partner services to all persons diagnosed with early (primary, secondary, early latent) syphilis or newly diagnosed with HIV infection. Some provide partner services for persons who may have cephalosporin-resistant gonorrhea. Fewer U.S. health departments routinely provide partner services to persons with gonorrhea, chlamydial infection, trichomoniasis, or other STIs; responsibility for ensuring the treatment of partners of persons with STIs other than syphilis and HIV often rests with the clinician and patient [4].

EXPEDITED PARTNER THERAPY

Effective management of patients with highly infectious but treatable STIs requires treatment of their current or recent sex partner(s) to prevent reinfection and further transmission. Expedited partner therapy differs from standard patient referral of their partner(s) by delivery of a prescription or appropriately packaged medication from the patient to their partner(s) without prior medical evaluation. The clinician should also give the patient written materials for their partner(s) that includes general education about the STI, notification the partner(s) may have been exposed, and information about the importance of treatment. These materials also should inform partners about potential therapy-related allergies and adverse effects, and symptoms that suggest complications. Expedited partner therapy bypasses the need for sex partner(s) to arrange and travel for an office visit and clinician evaluation. Providing medication is preferred because prescriptions may not be filled. Expedited partner therapy does not replace formal diagnosis, treatment, or referral, but should be available to clinicians as an option for partner treatment. Expedited partner therapy is especially beneficial when sex partner(s) have limited resources [32].

GENERAL TREATMENT CONSIDERATIONS

Several of the recommended steps in the process of diagnosing and treating patients with STIs are common to all or multiple STIs. All patients should be given detailed information on the natural history, transmission, treatment, and complications relevant to their diagnosed STI. Patients should also be provided with clear, accurate written information and directed to appropriate web-based patient information. All patients seeking evaluation or treatment for an STI should be tested for HIV infection.

ANTIMICROBIAL SUSCEPTIBILITY TESTING

Culture tests are used for antimicrobial susceptibility testing. These may be ordered following an apparent treatment failure to determine if an antibiotic-resistant strain is culpable, so treatment can be initiated with an alternative agent. The CDC recommends several methods for this testing in STIs. The examples below are culture tests used in gonorrheal infection.

Disk Diffusion Test

With disk diffusion testing, antibiotic-impregnated paper disks determine antimicrobial resistance of a bacterial isolate. The disks are placed on a lawn of bacterial growth, and micro-organisms that grow closer to a disk are more resistant to the antibiotic on the disk [33].

Broth Dilution and Agar Dilution Methods

Broth dilution and agar dilution methods test a bacterial isolate against a range of antimicrobial concentrations. These are similar to disk diffusion but use plastic strips with an antibiotic gradient indicating the antibiotic concentration at different points on the strip. The minimal inhibitory concentration (MIC), the lowest concentration of drug that inhibits organism growth, is read at the point where the border of growth inhibition intersects the strip [33].

APPROACHES TO TREATMENT

The goals of STI treatment are four-fold: eradicate infection; alleviate symptoms and signs; decrease risk of complications such as infertility, chronic pain, and dissemination of disease; prevent transmission [4]. In order to assure patient adherence and/or guarantee treatment exposure, oral therapies should be provided on-site with the first dose directly observed, regardless of whether the regimen is single- or multiple-dose [4]. Presumptive treatment on initial visit is recommended for patients with suspected chlamydia, gonorrhea, and syphilis, even before laboratory test results are available for confirmation. This is essential because early treatment decreases transmission risk, and some patients may not be able to follow through with a second visit and remain infected [4].

The CDC has proposed guidelines for the use of doxycycline post-exposure prophylaxis (PEP) for prevention of bacterial STIs, because it has demonstrated benefit in reducing chlamydia, gonorrhea, and syphilis infections and represents a new approach to addressing STI prevention in populations at increased risk for these infections [148]. Most research supporting this use has involved a dose of 200 mg administered within 24 to 72 hours of condomless sex. Doxycycline PEP, when offered, should be implemented in the context of a comprehensive sexual health approach including risk reduction counseling, STI screening and treatment, recommended vaccination, and linkage to HIV pre-exposure prophylaxis (PrEP), HIV care, or other services, as appropriate [148].

FOLLOW-UP

High recurrence rates occur several months after initial treatment of chlamydia, gonorrhea, and other STIs, even in patients who are treatment adherent. Infection after a standard treatment regimen is usually due to re-infection by an untreated or new sex partner, which elevates risks for transmission and adverse outcomes. For many STIs and especially for chlamydia, gonorrhea, and syphilis, patients should be retested three months post-treatment—regardless of whether they believe their sex partners were treated or cleared of infection. If this is not possible, patients should be retested during the next clinic visit [4; 34].

In the United States, confirmed cases of chlamydial infection, gonorrhea, and syphilis must be reported to the state or local public health department.

CHLAMYDIA

Chlamydia is a bacterial infection caused by *C. trachomatis* and may result in urethritis, epididymitis, cervicitis, acute salpingitis, or other syndromes when sexually transmitted; however, the infection is often asymptomatic in women [1]. Chlamydia is highly prevalent in the general population, particularly among young women. Multiple sequelae may result from *C. trachomatis* infection in women, the most serious of which include PID, ectopic pregnancy, and infertility. With *C. trachomatis*, serotypes D–K cause urogenital infection and serovars L1–L3 cause lymphogranuloma venereum [36].

The main route of infection is through penetrative sexual intercourse, but chlamydia can be detected in the conjunctiva and oropharynx without genital infection. *Chlamydia* infection is highly transmittable. Up to 75% of persons become infected by sex partners with chlamydia, but with asymptomatic infection the norm in men and women, most infected persons are unaware of their status. As noted, up to 30% of untreated women develop PID and associated infertility, debilitating chronic pelvic pain, or life-threatening tubal pregnancy. Chlamydia and other inflammatory STIs can facilitate HIV transmission. Infected pregnant women can transmit *Chlamydia* to their infants during delivery, potentially leading to pneumonia and ophthalmia neonatorum, a cause of blindness [27; 36].

CLINICAL FEATURES

Asymptomatic chlamydia infection is common among both men and women; spontaneous remission without treatment occurs within one year in up to 45% of asymptomatic patients [37]. Annual screening of all sexually active women younger than 25 years of age is recommended, as is screening of older women with new or multiple sex partners [4]. Symptoms and signs vary by sex. In either men or women, chlamydia can be transferred to the eye (acute conjunctivitis). An infrequent complication, reactive arthritis, is an immunologic reaction to genital or intestinal infection that can cause skin or eye lesions and noninfectious recurrent urethritis [4].

Women

Common symptoms in women include vaginal discharge, post-coital and intermenstrual bleeding, dysuria, lower abdominal pain, and deep dyspareunia. Physical exam can reveal pelvic and/or cervical motion tenderness; cervicitis (yellow, mucopurulent exudate with/without contact bleeding); or cervical ectopy (expansion of red endocervical epithelium onto vaginal surfaces of cervix) [36; 38].

Men

Symptoms in men include urethral discharge, dysuria, urethritis (acute severe onset dysuria, frequency, and copious, purulent discharge mimicking gonococcal urethritis), and possible progression to epididymitis [36; 38].

DIAGNOSIS

Chlamydia requires definitive diagnosis, because signs and symptoms resemble gonorrhea, and both infections require distinct antibiotic treatment approaches. Given the symptom overlap, *Neisseria gonorrhoeae* and *C. trachomatis* are often tested together [27].

NAAT is the method of choice in chlamydia testing, because it has greater sensitivity and specificity than other chlamydia tests. Specimens should be obtained from vulvovaginal swab in patients with a vagina, first-catch urine in patients with a penis, rectal swab in MSM or those who frequently receive anal sex, and oropharyngeal swab for oropharyngeal infection [27; 39].

TREATMENT

Chlamydia treatment should be promptly delivered to all persons testing positive, because delayed treatment is associated with PID and other complications [38]. Recommended treatment is summarized in ***Table 3.***

Early studies demonstrated that azithromycin and doxycycline had comparable efficacy in urogenital chlamydial, with microbial cure rates of 97% and 98%, respectively [40]. Randomized trials and observational studies published in the past decade have found that microbiologic treatment failure among men is higher for azithromycin than for doxycycline, and among men and women doxycycline is more efficacious than azithromycin for rectal *C. trachomatis* infection [4]. A randomized trial for the treatment of rectal chlamydia infection among MSM found that the microbiologic cure was 100% with doxycycline and 74% with azithromycin [59]. Oropharyngeal chlamydia can be sexually transmitted to genital sites and should be treated with doxycycline [4; 43; 44].

TREATMENT OF CHLAMYDIAL INFECTIONS		
Patient Population	**Treatment Regimen**	
	Recommended	**Alternative**
General	Doxycycline 100 mg oral twice daily for 7 days	Any one of the following: • Azithromycin 1 g oral single-dose • Levofloxacin 500 mg oral daily for 7 days
Pregnant women	Azithromycin 1 g oral single-dose	Amoxicillin 500 mg oral three times per day for 7 days
Source: [4]		*Table 3*

Test-of-cure four weeks after completion of therapy to detect treatment failure should be performed when adherence is in question, symptoms persist, or reinfection is suspected [4]. Completing chlamydial NAAT less than three weeks post-therapy increases the risks of false-positive results and is not recommended [27; 45]. When recurrent active chlamydia infection is observed in women or men treated for chlamydia in preceding months, it is unlikely to represent treatment failure but rather reinfection caused by failure of sex partners to receive treatment, or re-exposure from a newer infected partner [4]. This highlights the need for improved education and treatment of sex partners.

Treatment During Pregnancy

Doxycycline is contraindicated in the second and third trimesters, and animal studies have raised concerns over ofloxacin and levofloxacin [46]. Azithromycin is safe and effective as an alternative drug for chlamydia in pregnancy [47; 48]. All pregnant women diagnosed with chlamydia should be retested three months after treatment. Women younger than 25 years of age and those at increased risk for chlamydia should be rescreened during the third trimester [49].

Amoxicillin (500 mg orally three times per day for seven days) is the preferred alternative therapy in pregnancy with persistent chlamydial symptoms following exposure to penicillin-class antibiotics [50]. Gastrointestinal side effects from erythromycin can lead to nonadherence, and lower-dose 14-day regimens can mitigate gastrointestinal intolerance. The potential hepatotoxicity of erythromycin estolate contraindicates its use in pregnancy [4].

GONORRHEA

Gonorrhea results from infection by the bacterium *N. gonorrhoeae* and can affect the cervix, uterus, and fallopian tubes in women, and the urethra, mouth, throat, eyes, and anus of both sexes and manifest as urethritis, cervicitis, proctitis, salpingitis, or pharyngitis [1]. If untreated, gonococcal infection may disseminate to distant sites (e.g., joints) and become a life-threatening illness [51; 52]. At an estimated 820,000 new infections annually, gonorrhea is the second most commonly reported bacterial STI in the United States [34].

N. gonorrhoeae has developed resistance to almost every antimicrobial agent used against it. This highly concerning aspect of gonorrhea control is discussed later in this course.

To effectively counter rising rates of gonorrheal infection and the probability of further antimicrobial drug resistance, a 2017 paper states that such efforts require an understanding of why gonorrhea is so common in MSM. Unlike heterosexual men and women, gonorrheal infection is most commonly found in the pharynx and rectum in MSM, is highly likely to be asymptomatic (in contrast to urethral infection), and given the persistence and

lack of symptoms with infection in these sites, oral-oral contact (kissing) and oral-anal sex are believed to be driving increasing gonorrheal infection rates among MSM [53].

CLINICAL FEATURES

The most common symptoms of gonorrhea are purulent discharge from the penis or cervix and painful or difficult urination. As with chlamydia, the most serious complications occur in women. Untreated gonorrhea can lead to PID and increased risk of HIV infection in both sexes. Mothers who acquire gonorrhea during pregnancy can pass the infection to the fetus, possibly causing blindness or life-threatening infections [51; 52].

Urethral gonorrheal symptoms can cause men to seek curative treatment in time to prevent sequelae but not transmission. Gonococcal infections are often asymptomatic in women, or recognizable symptoms may not appear until complications develop such as PID [28]. Signs and symptoms of gonorrhea include [54]:

Women

- Bleeding between menstrual periods and after sexual intercourse
- Pain in the abdomen, during intercourse or urination
- Abnormal vaginal discharge
- Frequent urination

Men

- White, yellow, or greenish discharge from penis
- Pain or burning when urinating
- Pain, tenderness, or swelling of testes

DIAGNOSIS

Testing for gonorrhea and chlamydia together is increasingly recommended [27; 54]. NAAT is the preferred method because it offers greater sensitivity and specificity than other gonorrhea tests, analyzes the widest range of extragenital specimens, and eliminates the need for pelvic exam in women [27; 54].

Gram stain and culture of urethral discharge or swab specimens can diagnose gonorrhea in symptomatic men, but it is inaccurate in detecting non-gonococcal infection in asymptomatic men and gonorrheal infection in women [54]. Culture testing is effective for detecting rectal, oropharyngeal, and conjunctival gonococcal infection [27; 55; 56]. With suspected or documented treatment failure, clinicians should request NAAT testing and submit specimens for culture and antimicrobial susceptibility testing [4]. The CDC recommends that all individuals with suspected gonorrhea should also be evaluated for chlamydia, syphilis, and HIV infection [4].

TREATMENT

Uncomplicated Gonococcal Infections

Recommended and alternative treatment approaches for all gonorrheal infection sites and stages are summarized in ***Table 4***. Ceftriaxone plus azithromycin is the only first-line recommendation for urogenital, endocervical, anorectal, and oropharyngeal gonorrheal infection and for gonorrheal infection in pregnant women and patients with HIV [34; 58]. This arose from efforts by the CDC to prevent development of cephalosporin resistance, following evidence during 2006–2011 suggesting decreasing efficacy with cefixime against *N. gonorrhoeae* [34]. Prior to December 2020, the CDC recommended dual ceftriaxone/azithromycin therapy. However, it shifted to a recommendation for ceftriaxone monotherapy to help combat increasing resistance to azithromycin [63]. Cefixime was removed as a first-line treatment of gonorrhea in 2012 [57]. Single-dose ceftriaxone should be combined with doxycycline, 100 mg daily for seven days, unless chlamydia infection has been excluded [4].

Single-injection ceftriaxone 500 mg provides sustained, high bactericidal levels in the blood. In clinical trials, ceftriaxone showed cures in 99.2% of uncomplicated urogenital and anorectal infections and 98.9% of pharyngeal infections [61; 62]. Other single-dose injectable cephalosporins are available but not recommended as gonorrhea treatment. Gentamicin is solely recommended for use when ceftriaxone is unavailable.

TREATMENT OF GONOCOCCAL INFECTIONS		
Site of Infection	**Treatment Regimen**	
	Recommended	**Alternative**
Uncomplicated infection		
Cervix, urethra, or rectum	Single-dose ceftriaxone 500 mg IM[a]	Single-dose gentamicin 240 mg IM PLUS azithromycin 2 g orally OR single-dose cefixime 800 mg orally
Pharynx		—
Pregnancy		Consult infectious disease specialist
Gonococcal conjunctivitis	Single-dose ceftriaxone 1 g IM	—
Disseminated infection		
Arthritis and arthritis-dermatitis syndrome	Ceftriaxone 1 g IM or IV every 24 hours	Cefotaxime 1 g IV every 8 hours OR ceftizoxime 1 g every 8 hours
Gonococcal meningitis and endocarditis	Ceftriaxone 1–2 g IV every 24 hours	—
[a]A dose of 1 g IM should be used for patients weighing 150 kg or more.		
Source: [4; 34; 63]		*Table 4*

Patients with a history of IgE-mediated beta-lactam allergy, including anaphylaxis, should be considered for penicillin skin testing, although cross-reactivity to third-generation cephalosporins (ceftriaxone) is very low [64; 65; 66].

Follow-Up

Dispense on-site and observe first dosing for all prescribed treatment. If medications are not available when treatment is indicated, linkage to an STI treatment facility should be provided for same-day treatment [4].

All sex partners within 60 days of diagnosis should be evaluated and presumptively treated for *N. gonorrhoeae* and *C. trachomatis* infections. If the last potential exposure was more than 60 days previous, the most recent sex partner should be treated. Patients and sex partners should abstain from condomless sexual activity for seven days after treatment and until sex partners are adequately treated [4]. Under current guidelines, every effort should be made to ensure that a patient's sex partners are evaluated and treated with the recommended regimen (a single dose of ceftriaxone 500 mg IM). If a healthcare provider cannot ensure an infected patient's partner will be promptly linked to care, expedited partner therapy with a single 800-mg dose of cefixime may be delivered to the partner by the patient, a disease investigation specialist, or collaborating pharmacy [4; 32]. If a chlamydia infection in the patient has not been excluded, doxycycline 100 mg twice daily for seven days should be added to the sex partner's regimen. When cephalosporin treatment failure is suspected, the treating clinician should consult an infectious disease specialist, an STI/HIV Prevention Training Center clinical expert, the local or state health department STI program, or the CDC for advice [67].

All patients should be retested within three months of initial treatment [34]. A test-of-cure using either culture or NAAT is recommended in patients with pharyngeal gonorrhea 14 days after treatment with an alternative regimen. If the NAAT is positive, confirm by culture testing before retreatment. All positive test-of-cure cultures should include antimicrobial susceptibility testing. Symptoms that persist after treatment should be evaluated by culture, with or without NAAT, and any gonococci isolated should be tested for antimicrobial susceptibility [4].

Gonococcal Conjunctivitis

Gonococcal conjunctivitis is uncommon and research data on gonococcal conjunctivitis treatment in adults are limited. Consider one-time lavage of the infected eye with saline solution and consultation with an infectious disease specialist [4].

Disseminated Gonococcal Infection

Disseminated gonococcal infection frequently appears as petechial or pustular acral skin lesions, asymmetric polyarthralgia, tenosynovitis, or oligoarticular septic arthritis. The infection can be complicated by perihepatitis and rarely by endocarditis or meningitis. Some *N. gonorrhoeae* strains that cause disseminated infection are associated with minimal genital inflammation [68]. If disseminated gonococcal infection is suspected, use NAAT or culture specimens from urogenital and extragenital sites, and specimens from disseminated infection sites such as the skin, synovial fluid, blood, and central nervous system (CNS). Test all *N. gonorrhoeae* isolates for antimicrobial susceptibility [4].

Hospitalization and consultation with an infectious disease specialist are initially recommended, especially when treatment adherence is doubted, diagnosis uncertain, or purulent synovial effusions or other complications are present. Examine for evidence of endocarditis and meningitis [4].

Arthritis and Arthritis-Dermatitis Syndrome

When treating the arthritis-dermatitis syndrome, switch to an oral agent according to antimicrobial susceptibility testing 24 to 48 hours after substantial clinical improvement, for total treatment of at least seven days [4].

Gonococcal Meningitis and Endocarditis

The optimal treatment and duration for disseminated gonococcal infection is poorly studied. Antimicrobial susceptibility results direct the treatment of disseminated gonococcal infection, but pending susceptibility results, treatment should be guided by the clinical presentation. Meningitis treatment should continue for 10 to 14 days. Parenteral antimicrobial therapy for endocarditis should continue for more than four weeks [4].

SYPHILIS

Syphilis is a multistage, multisystem STI caused by infection with *Treponema pallidum*, a spirochete (i.e., a treponeme) bacterium. Transmission occurs through direct contact with an infectious chancre (lesion) or through vertical transmission during pregnancy. The site of bacterial entry in heterosexual patients is typically genital. In MSM, extragenital sites (e.g., anal, rectal, oral) infected through oral-anal or genital-anal contact account for 32% to 36% of transmissions [69]. The clinical course is highly variable [1].

Syphilis infection in pregnant women increases the risk of miscarriage, stillbirth, and fetal transmission during pregnancy or delivery (congenital syphilis), which can result in skeletal deformity, abnormal speech or motor development, seizures, anemia, liver disease, or neurologic disorders [52]. Full discussion of syphilis infection in pregnant women and congenital syphilis in newborns is outside the scope of this course.

CLINICAL FEATURES

Untreated syphilis can progress through stages of primary, secondary, latent (early and late), and tertiary disease. Syphilis is infectious and transmittable during early disease (primary, secondary, early latent). Clinical manifestations of syphilis vary by stage [7; 51; 52; 69; 70].

Primary Infection

After an average incubation of 21 days (range: 9 to 90 days), a painless chancre or ulcer appears at the anogenital infection site, with regional lymphadenopathy. The ulcer resolves in three to eight weeks by local immune clearance, after the bacteria have widely disseminated through blood and lymphatic systems.

Secondary Infection

Rash, mucocutaneous lesions, and generalized lymphadenopathy, the "classical triad" reflecting multisystem involvement, develop 4 to 10 weeks after the initial chancre [71]. Roughly 1% to 2% of patients develop neurologic complications during secondary syphilis.

Latent Infection

The disease becomes asymptomatic following spontaneous resolution of secondary syphilis 3 to 12 weeks from onset. The first year is termed early latent, and afterward, late latent. Early latent syphilis is considered infectious because secondary disease recurs in 25% of patients [70].

Tertiary (Late) Infection

Tertiary (late) syphilis occurs 10 to 40 years after initial infection in 33% of untreated patients. Inflammatory lesions can develop in bone (osteitis), skin (gummatous lesions), connective tissues of the cardiovascular system (aortitis, coronary vessel disease), and less often, in the respiratory tract, reproductive organs, lymph nodes, liver, or brain/CNS. This stage is potentially fatal.

Neurosyphilis

Neurosyphilis results from CNS infection by *T. pallidum* and can occur at any syphilis stage. Early neurosyphilis manifests in the initial months or years of infection in cranial nerve dysfunction, meningitis, stroke, altered mental status, and auditory or ophthalmic abnormalities. Late neurosyphilis manifests 10 to 30 years after primary disease as progressive dementia or paralysis with brain and/or spinal cord involvement; optical involvement manifests as syphilitic uveitis, neuroretinitis, optic neuritis, and possibly blindness.

Infection of the visual system (ocular syphilis) or auditory system (otosyphilis) can occur at any stage of syphilis but is commonly identified during the early stages and can present with or without additional CNS involvement [4]. Ocular syphilis often presents as panuveitis, but limited forms are common, including conjunctivitis, anterior uveitis, posterior uveitis, optic neuropathy, and retinal vasculitis. Otosyphilis presents with combined cochlear and vestibular symptoms, including tinnitus, vertigo, and sensorineural hearing loss (unilateral or bilateral, rapid onset and progression).

DIAGNOSIS

Diagnostic Testing

Darkfield examinations and molecular tests for detecting *T. pallidum* directly from lesion exudate or tissue are definitive methods for diagnosing early syphilis [4]. In later stages or when lesions are absent, infection is diagnosed using serologic assays that detect antibodies in serum or cerebrospinal fluid (CSF). Different tests are used for detecting treponemal-specific antibodies against *T. pallidum* or nontreponemal antibodies against *T. pallidum* and similar infection. Both types of tests are required for diagnostic accuracy. The use of only one type of serologic test (nontreponemal or treponemal) is insufficient for diagnosis and can result in false-negative results among persons tested during primary syphilis and false-positive results among persons without syphilis or those previously treated [4]. Aside from patients with suspected neurosyphilis, other testing is not needed. Antibody tests may also be used to measure treatment response [30; 72].

Patients may be negative for antibodies against *T. pallidum* in primary syphilis, especially in the first two weeks after symptom onset. With progression into secondary syphilis, antibodies to *T. pallidum* reach peak titers and may persist indefinitely regardless of disease state or prior therapy. To help differentiate active from past syphilis infection, tests are used to detect antibodies against nontreponemal antigens such as cardiolipin, a lipid antigen released by host cells damaged by *T. pallidum*. Nontreponemal antibodies are typically positive during current infection and negative following treatment or during late/latent syphilis [73].

Nontreponemal antibody tests are highly sensitive but low in specificity to *T. pallidum*, and false-positives can result from other conditions such as autoimmune disease, tuberculosis, or HIV. For the diagnosis of syphilis, a positive test result must be confirmed by a treponemal test. Common nontreponemal antibody tests include [30; 72; 74]:

- Rapid plasma regain (RPR): The most widely used NNT, accurate for screening and confirming positive treponemal testing, and sensitive to treatment response

- Venereal disease research laboratory (VDRL): The only FDA-approved NNT assay for CSF specimens, but otherwise replaced by RPR
- Toluidine red unheated serum test (TRUST): A modified version of VDRL with use similar to RPR

Treponemal antibody tests are highly specific to *T. pallidum*. The majority of patients who test positive will have reactive treponemal tests for the remainder of their lives, regardless of adequate treatment and independent of disease activity [4]. However, 15% to 25% of patients treated during the primary stage revert to being serologically nonreactive after two to three years. Treponemal antibody titers do not predict treatment response and should not be used for this purpose. Nontreponemal antibodies disappear around three years after successful treatment, and positive treponemal tests require NNT confirmation to distinguish active infection (or reinfection) from previous resolved illness. Treponemal antibody tests include [30; 70; 72; 74]:

- Fluorescent treponemal antibody absorption (FTA-ABS): Useful three to four weeks after exposure; measures antibodies in CSF to help diagnose neurosyphilis.
- *T. pallidum* particle agglutination assay (TP-PA): Greater specificity and fewer false positives can make it preferred over FTA-ABS.
- Microhemagglutination assay (MHA-TP): A less common confirmatory method.

Immunoassays may also be used to diagnose syphilis. Options include enzyme, multiplex flow, chemiluminescent, and microbead immunoassays.

Historically, serologic testing for syphilis used initial NNT screens such as the RPR, with positive results followed by FTA-ABS or TP-PA for confirmation. Although accurate, this analytic process is labor intensive and requires subjective interpretation by laboratory personnel [73].

Using enzyme or multiplex flow immunoassay to detect immune antibodies produced against *T. pallidum* (IgG, IgM, or IgG/IgM) is more popular today. These assays are highly sensitive and specific and allow objective interpretation of results and higher throughput [73; 74].

The Mayo Clinic now performs syphilis screening by first using multiplex flow immunoassay to detect *T. pallidum*-specific IgG antibodies. IgG antibodies to syphilis can remain elevated despite appropriate antimicrobial treatment, and a reactive result does not distinguish recent from past infection. A positive multiplex flow immunoassay is followed by NNT testing using RPR; this provides supplemental serologic data, and indicators of syphilis disease state and treatment history [73].

Latent Syphilis

Latent syphilis is often identified after positive serologic testing in a patient without other obvious signs of disease. All such patients should be evaluated for secondary stage disease, including physical examination of accessible mucosal surfaces (e.g., oral cavity, perianal area, perineum and vagina in women, underneath the foreskin in uncircumcised men) for mucosal lesions [69].

Tertiary Syphilis

Limited information is available concerning clinical response and follow-up of patients with tertiary syphilis. They should be managed in consultation with an infectious disease specialist [4].

Neurosyphilis

Serologic testing is used to support a neurosyphilis diagnosis, but no single test has uniform specificity. Diagnosis is based on the combination of CSF abnormalities (e.g., CSF cell count, protein abnormality, reactive CSF-VDRL), systemic serologic test results, and neurologic signs and symptoms [75].

Patients of any syphilis stage and HIV status should be followed closely for new-onset symptoms and signs of neurologic (e.g., cognitive dysfunction, motor or sensory deficits, meningitis, stroke, hearing loss, cranial nerve palsies) or ophthalmic (e.g., uveitis, iritis, neuroretinitis, optic neuritis) disease. Evaluate suspected patients with CSF analysis, otologic exam, and ocular slit-lamp ophthalmologic exam [70; 72].

TREATMENT OF SYPHILIS INFECTIONS		
Infection Stage or Patient Group	**Treatment Regimen**	
	Recommended	**Alternative**
Primary, secondary, or early latent infection with or without HIV co-infection	Single-dose benzathine penicillin G 2.4 million units IM	—
Late/latent infection of unknown duration	Benzathine penicillin G 7.2 million units IM total, given in 3 doses of 2.4 million units at one-week intervals	—
Tertiary[a]		
Late/latent infection with HIV co-infection		
Neurosyphilis or ocular syphilis with or without HIV co-infection	For 10 to 14 days: Aqueous crystalline penicillin G 18–24 million units IV per day, given in doses of 3–4 million units every 4 hours or continuous infusion	For 10 to 14 days: Procaine penicillin G 2.4 million units IM once daily, plus probenecid 500 mg oral four times per day
During pregnancy	Treat according to infection stage	
[a]In patients not allergic to penicillin and without evidence of neurosyphilis.		
Source: [4]		*Table 5*

When ocular manifestations are present, CSF examination is warranted even if other clinical neurologic findings are negative. Patients with known or suspected ocular syphilis should be referred to an ophthalmologist and treated for neurosyphilis even with normal CSF findings. In cases of ocular syphilis and abnormal CSF parameters, follow-up CSF studies are helpful in assessing response to treatment [4].

In early-stage syphilis, CSF abnormalities have been observed in association with negative clinical neurologic findings. In this context, abnormal CSF findings do not alter recommended treatment protocols [70; 72].

Comorbid HIV Infection

HIV infection does not change treponemal and NNT diagnostics, but patients with advanced HIV infection/immunosuppression are more likely to have clinical and CSF abnormalities consistent with neurosyphilis [69].

TREATMENT

Penicillin G, administered parenterally, is the preferred antibiotic for treating patients with any stage of syphilis. The specific penicillin regimen (preparation, dosage, and duration of treatment) depends on the stage and clinical manifestations of disease. Other considerations include the presence of comorbidities and pace of clinical response (***Table 5***). Penicillin G is also the only known effective antimicrobial for preventing maternal transmission of syphilis to the fetus and for treating fetal infection [76]. Parenteral is favored over the oral route because therapy is supervised, and bioavailability is guaranteed. However, deep IM injections of benzathine and procaine penicillin are painful; 1% lidocaine can be added to the injection for pain reduction [69]. Patients should be asked about known penicillin allergy before treatment. An infectious disease consultation is advisable when treating any patient with penicillin allergy. A 2010 clinical trial found azithromycin as effective as penicillin IM for curing early-stage syphilis in patients without HIV. This was an important breakthrough for settings with limited resources and patients with penicillin allergic reactions [51; 52].

According to the Minnesota Department of Health, penicillin G administered intramuscularly or intravenously is the preferred drug for treating all stages of syphilis.

(https://www.health.state.mn.us/diseases/syphilis/hcp/protocol.pdf. Last accessed April 24, 2023.)

Level of Evidence: Expert Opinion/Consensus Statement

Penicillin effectiveness as syphilis treatment was established through clinical experience before clinical trials confirmed its efficacy. Almost all current syphilis treatments are based on laboratory considerations, biologic plausibility, expert opinion, case studies, and decades of clinical experience [69]. Clinical trial data are lacking on optimal penicillin selection and non-penicillin regimens [4].

The duration of penicillin activity at treponemicidal levels should be at least seven days to cover a sufficient number of treponeme division times (30 to 33 hours) in early syphilis. With longer treatment regimens, sub-treponemicidal intervals should not be longer than 24 to 30 hours [77; 78]. Longer treatment durations are used for late syphilis, because treponemes divide more slowly in late disease. Persistence of treponemes despite apparently successful treatment of late disease indicates that some may have been "resting" or dividing very slowly [69; 79]. The durations of the recommended and alternative regimens for neurosyphilis are shorter than the duration of the regimen used for latent syphilis. Therefore, benzathine penicillin, 2.4 million units IM once per week for one to three weeks, can be considered after completion of these neurosyphilis treatment regimens to provide a complete total duration of therapy [4].

Clinicians have inadvertently but widely prescribed combination benzathine-procaine-penicillin (Bicillin C-R) instead of the standard benzathine-penicillin product (Bicillin L-A). Benzathine, procaine, and oral penicillin combinations are inappropriate for syphilis treatment [80].

Treatment for primary, secondary, latent disease, or neurosyphilis does not differ for patients with HIV infection. For all patients, additional doses of benzathine penicillin G, amoxicillin, or other antibiotics do not enhance efficacy of early syphilis treatment, and recommended syphilis treatment is effective in preventing neurosyphilis [81]. Changes in CSF parameters can occur more slowly in patients with HIV, especially with advanced immunosuppression, but use of antiretroviral therapy may improve clinical outcomes in patients with HIV and syphilis [82; 83; 84; 85].

Jarisch-Herxheimer reaction (JHR) is an acute febrile reaction with headache, myalgia, fever, and other symptoms that develops in the first 24 hours of starting syphilis therapy. Patients should be informed about this possible adverse reaction and its management. JHR is most frequent in persons with early syphilis, and antipyretics can be used to manage symptoms [4].

Treatment of Syphilis During Pregnancy

Pregnant women should be treated with the penicillin regimen appropriate for their stage of infection. Pregnant women with syphilis in any stage who report penicillin allergy should be desensitized and treated with penicillin [4]. The desensitization process will be discussed in more detail later in this course.

FOLLOW-UP

Primary and Secondary Syphilis

CDC guidelines recommend follow-up clinical and serologic evaluation at 6 and 12 months after treatment; more frequent evaluation should be considered if opportunity is uncertain or repeat infection is a concern [4]. Patients with HIV should be clinically and serologically evaluated at 3, 6, 9, 12, and 24 months post-therapy, and in all patients with neurosyphilis, at 6, 12, 18, and 24 months post-therapy [82; 83]. Treatment failure or re-infection is likely in patients with persistent or re-emerging signs or symptoms or a fourfold (or greater) increase in nontreponemal test titer for more than two weeks. Patients should be treated, HIV infection retested, and a CSF exam performed to help distinguish treatment failure from reinfection [4].

Optimal management with a less than fourfold decline in post-treatment titers is unclear. At a minimum, one should provide additional clinical and serologic follow-up and retest for HIV infection. Other considerations include a repeat course of treatment when follow-up cannot be ensured, and CSF exam to rule out unrecognized CNS infection. With negative CSF results, weekly injection of benzathine penicillin G 2.4 million units IM for three weeks is recommended [4].

By 6 to 12 months post-treatment, failure of nontreponemal test titers to decline fourfold can indicate treatment failure. However, at one-year post-treatment, 15% to 20% of treated primary and secondary syphilis patients will not achieve the fourfold decline in nontreponemal titer that defines response [81; 86].

After 24 months, if nontreponemal titers fail to decline fourfold, CSF exam can be considered and treatment administered accordingly, although low initial titers (<1:8) might not decline [86; 87; 88].

When serologic titers fail to decline despite repeated courses of therapy for primary, secondary, or latent syphilis and negative CSF exams, the need for additional therapy or repeat CSF exam is unclear but is generally not recommended. Serologic response to treatment is also influenced by syphilis stage (with earlier stages more likely to decline fourfold and become negative), initial nontreponemal antibody titers (with lower titers less likely to decline fourfold than higher titers), and previous syphilis treatment (in whom nontreponemal titers decline more slowly) [86; 87; 88].

The appropriate course of action is also unclear for a missed weekly penicillin dose. Clinical experience suggests a 10- to 14-day interval between benzathine penicillin doses for latent syphilis may be acceptable before restarting the injection sequence. Pharmacologic considerations suggest a seven- to nine-day interval between doses, if feasible, is more optimal [77; 78; 79]. Missed doses are unacceptable in pregnant women treated for latent syphilis, and the full therapy course must be repeated with any missed dose [89].

Latent and Tertiary Syphilis

Clinical follow-up and repeat nontreponemal antibody test assays at 6, 12, and 24 months, and CSF exam if observing the following [81]:

- A fourfold or greater increase in titer for more than two weeks
- Initially high titer (≥1:32) failing to decline at least fourfold within 12 to 24 months of therapy
- Clinical signs or symptoms of syphilis
- If CSF parameters are abnormal, treat for neurosyphilis; if normal, re-treat for latent syphilis.

Neurosyphilis

Data from studies cited in CDC guidelines indicate that, among immunocompetent persons and persons with HIV infection who are on effective antiretroviral therapy, normalization of the serum RPR titer predicts normalization of abnormal CSF parameters after neurosyphilis treatment [4; 83; 84]. Therefore, repeated CSF examinations are unnecessary when such patients exhibit serologic and clinical responses after treatment. Otherwise, if a satisfactory response to treatment is in question, repeat CSF examination may be prudent at six-month intervals. If CSF parameters have not normalized within 24 months, a repeat course of penicillin should be considered.

Management of Sex Partners

Sexual transmission of *T. pallidum* is thought to occur when mucocutaneous syphilitic lesions are present, which this is uncommon after the first year of infection. Persons sexually exposed to a patient diagnosed with primary, secondary, or early latent syphilis should be evaluated clinically and serologically and treated [4]. Anyone exposed to a sex partner within 90 days of diagnosis should be treated presumptively for early syphilis, even when serologic testing is negative. Anyone exposed to a sex partner more than 90 days before diagnosis should be treated presumptively for early syphilis if serologic test results are not immediately available and follow-up opportunity uncertain. If serologic tests are negative, no treatment is needed. If serologic tests are positive, deliver treatment based on clinical and serologic evaluation and syphilis stage.

LYMPHOGRANULOMA VENEREUM

Lymphogranuloma venereum is caused by infection with L1, L2, or L3 serovars of *C. trachomatis*, resulting in a disease characterized by genital lesions, suppurative regional lymphadenopathy, or hemorrhagic proctitis. The infection is usually sexually transmitted [1]. The L1–L3 strains differ from chlamydial serotypes that cause trachoma, inclusion conjunctivitis, urethritis, or cervicitis in that they can invade and reproduce in regional lymph nodes. L2 is the most identified serovar in modern North American lymphogranuloma venereum outbreaks [91].

Lymphogranuloma venereum is endemic in parts of Africa, India, Southeast Asia, South America, and the Caribbean but occurs sporadically in the United States. Most patients diagnosed with lymphogranuloma venereum are MSM. Lymphogranuloma venereum has been a non-reportable STI in the United States since 1994, and prevalence rates are difficult to estimate. However, lymphogranuloma venereum has been tracked since 2004 in the UK, where 99% of lymphogranuloma venereum cases occur in MSM, frequently involved in dense sexual networks associated with the sex party scene and without obvious link to known lymphogranuloma venereum-endemic countries. MSM show a strong association between HIV and lymphogranuloma venereum, and compared with MSM with rectal chlamydial infection, those with rectal lymphogranuloma venereum are more likely to have proctitis symptoms and HIV infection [91; 92; 93].

CLINICAL FEATURES

Lymphogranuloma venereum infection disseminates from the mucosa via underlying tissue to regional lymph nodes, an infectious process that contrasts with chlamydial infection that is limited to the mucosa [91]. The clinical course of lymphogranuloma venereum is classically divided into three stages.

Stage 1 typically begins after a three-day incubation period with a small genital ulcer or papule at the site of entry. The lesion may cause ulceration of the overlying skin but often disappears by the time patients seek care [95; 96].

Stage 2 usually begins roughly two to four weeks later, with the inguinal lymph nodes on one or both sides enlarging and forming large, tender, sometimes fluctuant masses (buboes). The buboes stick to deeper tissues and cause the overlying skin to become inflamed, sometimes with fever and malaise. In women, backache or pelvic pain is common; the initial lesions may appear on the cervix or upper vagina, resulting in enlargement and inflammation of deeper perirectal and pelvic lymph nodes. Multiple draining sinus tracts may develop and discharge pus or blood [95; 96].

In stage 3, lesions heal with scarring, but sinus tracts can persist or recur. Persistent inflammation from untreated infection obstructs lymphatic vessels to cause swelling and skin sores [95; 96].

In MSM, hemorrhagic proctitis is the primary sign of transmission to the rectal mucosa. Patients may present with rectal pain, anorectal bleeding, mucoid and/or hemopurulent rectal discharge, tenesmus, constipation, and other symptoms of lower GI inflammation. Systemic symptoms can include fever and malaise [94; 97]. Outbreaks of lymphogranuloma venereum proctocolitis have occurred in some MSM communities. If not treated early, lymphogranuloma venereum proctocolitis can lead to chronic colorectal fistula and stricture, and reactive arthropathy has been reported [98].

In heterosexuals, lymphogranuloma venereum commonly manifests as tender unilateral inguinal and/or femoral lymphadenopathy. Rectal exposure in women can lead to proctocolitis that mimics inflammatory bowel disease. Clinical findings may include mucoid and/or hemorrhagic rectal discharge, anal pain, constipation, fever, and/or tenesmus [96]. Secondary bacterial infection or co-infection with another STI may develop in patients with genital or colorectal lymphogranuloma venereum lesions [4].

TREATMENT OF LYMPHOGRANULOMA VENEREUM		
Patient Population	**Recommended**	**Alternative**
General	Doxycycline 100 mg orally twice per day for 21 days	Erythromycin base 500 mg orally four times per day for 21 days OR azithromycin 1 g orally once weekly for 3 weeks

Source: [4] *Table 6*

DIAGNOSIS

Diagnosis is based on clinical suspicion, epidemiologic information, and exclusion of non-lymphogranuloma venereum etiologies when proctocolitis, inguinal lymphadenopathy, or rectogenital ulcers are present. Lymphogranuloma venereum is suspected in [27]:

- Individuals with genital ulcers, swollen inguinal lymph nodes, or proctitis
- Patients with buboes, which can be mistaken for abscesses caused by other bacteria
- Patients who have lived in, visited, or had sexual contact with persons from areas of endemic lymphogranuloma venereum

Diagnosis of lymphogranuloma venereum is based on isolation of *C. trachomatis* serotype L1, L2, or L3 in specimens from recto-genital lesions or lymph nodes. Specimens are tested for *C. trachomatis* by culture, direct immunofluorescence, or NAAT. Rectal specimen testing by NAAT for *C. trachomatis* is accurate, and MSM presenting with proctocolitis should have rectal specimens tested for chlamydia using NAAT. Diagnosis can also be made by detecting antibodies to chlamydial endotoxin (complement fixation titers >1:64 or microimmunofluorescence titers >1:256) or by genotyping using PCR-based NAAT [27].

TREATMENT

At initial evaluation and before chlamydia test results are available, patients with a clinical syndrome consistent with lymphogranuloma venereum (proctocolitis or genital ulcer and lymphadenopathy) should receive presumptive treatment for lymphogranuloma venereum (***Table 6***). Cases should be reported to the health department if required by state law [4].

Using NAAT to assess microbial cure, doxycycline (100 mg oral, twice daily for 21 days) for rectal lymphogranuloma venereum in MSM showed an average 98.5% cure rate in nine reviewed trials [91]. While doxycycline is effective for most patients, reports that abscess formation and rupture of lymphogranuloma venereum buboes have occurred during doxycycline therapy suggest that 21 days of doxycycline may be insufficient for clinical and microbial cure in more severe cases. These patients may require aspiration through intact skin or incision and drainage to prevent the formation of inguinal/femoral ulcerations [91].

Patients should be followed until signs and symptoms have resolved. All patients diagnosed with lymphogranuloma venereum should be tested for HIV, gonorrhea, and syphilis [4]. Treatment does not differ for patients with HIV, but these patients may have delayed symptom resolution and require prolonged therapy [4].

Treatment During Pregnancy

Fluoroquinolone-based treatments might be effective, but optimal treatment duration has not been evaluated. Pregnant and lactating women should be treated with erythromycin. Use of doxycycline in pregnancy might be associated with discoloration of teeth, but the risk is not well defined; doxycycline is compatible with breastfeeding. Azithromycin 1 g orally once weekly for three weeks is probably effective based on its antimicrobial activity with chlamydia, but data are lacking on its use in lymphogranuloma venereum during pregnancy [4; 46].

BACTERIAL VAGINOSIS

Bacterial vaginosis is the most common cause of abnormal vaginal discharge in women of childbearing age. Normally, hydrogen peroxide-producing lactobacilli are the dominant vaginal bacteria and maintain vaginal pH <4.5. In bacterial vaginosis, the pH rises above 4.5, up to 6.0. Lactobacilli remain present, but flora becomes dominated by anaerobic and facultative anaerobic bacteria in concentrations up to 1,000 times greater than normal. *Gardnerella vaginalis* and *Atopobium vagainae* are critical to bacterial vaginosis etiology; other commonly found bacteria belong to *Prevotella*, *Mobiluncus*, *Clostridiales*, *Leptotrichia*, and *Sneathia* species and *Mycoplasma hominis* [99; 100]. Risk factors for bacterial vaginosis include frequent vaginal douching, antibiotic use, poor hygiene, receptive oral sex, lack of condom use, multiple or a new sex partner, smoking, presence of STIs (chlamydia or herpes in particular), poorly controlled diabetes, dermatitis, and immune system disorders [102].

Whether bacterial vaginosis results from sexually transmitted pathogens is debated, but bacterial vaginosis places women at increased risk for complications from gynecologic surgery and pregnancy and infection with HIV, *N. gonorrhoeae*, *C. trachomatis*, and herpes simplex virus. Bacterial vaginosis increases the risk for HIV transmission to male sex partners. Bacterial vaginosis-associated bacteria can be found in the male genitalia, but treatment of male sex partners has not prevented recurrences [103; 104; 105].

CLINICAL FEATURES

The dominant bacterial vaginosis symptom is an unpleasant fishy smell, emitted by amines that increase vaginal pH and especially noticeable after vaginal intercourse. Examination shows a thin, white discharge coating the vaginal walls and vestibule. Bacterial vaginosis is not associated with soreness, itching, or irritation, and signs of inflammation are uncommon [102].

DIAGNOSIS

A bacterial vaginosis diagnosis is confirmed when at least three of Amsel clinical criteria are present [106]:

- Thin, white, homogeneous discharge smoothly coating the vaginal wall
- Clue cells (vaginal epithelial cells studded with adherent coccobacilli) on microscopy
- Vaginal fluid pH >4.5
- Release of a fishy odor from vaginal discharge by adding 10% potassium hydroxide (KOH) ("whiff test")

Gram stain determines the proportion of lactobacilli to gram-negative and gram-variable rods and cocci. The criteria are defined as follows [107]:

- Grade 1 (Normal): *Lactobacillus* morphotypes predominate
- Grade 2 (Intermediate): Mixed flora with lactobacilli, *Gardnerella*, or *Mobiluncus* morphotypes present
- Grade 3 (Bacterial vaginosis): *Gardnerella* and/or *Mobiluncus* morphotypes predominate; few/absent lactobacilli

TREATMENT

Treatment is recommended to alleviate vaginal symptoms and signs of infection (***Table 7***). Treatment may also reduce risks for acquiring *C. trachomatis*, *N. gonorrhoeae*, T. *vaginalis*, HIV, and herpes simplex type 2 [4].

Metronidazole, tinidazole, and clindamycin all show 70% to 80% cure rates at four-week follow-up. Oral metronidazole is established, well-tolerated, and inexpensive [108]. Intravaginal metronidazole gel and clindamycin cream have similar efficacy [109]. Metronidazole has a theoretical advantage of less activity against lactobacilli than clindamycin, while clindamycin is more active against most bacteria associated with bacterial vaginosis than metronidazole. Tinidazole is comparable to metronidazole in antibacterial activity and efficacy [110].

TREATMENT OF BACTERIAL VAGINOSIS		
Infection Stage	**Treatment Regimen**	
	Recommended	**Alternative**
Initial treatment	Any of the following: • Metronidazole 500 mg oral twice daily for 7 days • One full applicator (5 g) metronidazole gel 0.75% IVG daily for 5 days • One full applicator (5 g) clindamycin cream 2% IVG at bedtime for 7 days	Any of the following: • Tinidazole 2 g oral once daily for 2 days • Tinidazole 1 g oral once daily for 5 days • Clindamycin 300 mg oral twice daily for 7 days • One clindamycin ovule 100 mg IVG at bedtime for 3 days • Secnidazole 2 g oral granules in a single dose
First recurrence	Repeat initial treatment	—
Multiple recurrences	Either of the following: • Metronidazole IVG gel 0.75% twice weekly for more than three months or 750-mg suppository • Metronidazole or tinidazole 500 mg oral, twice per day for 7 days, followed by boric acid 600 mg IVG daily for 21 and metronidazole gel 0.75% twice weekly for 4 to 6 months	—
Suppressive therapy	Metronidazole oral 2 g plus fluconazole 150 mg monthly	—
IVG = intravaginal.		
Source: [4]		*Table 7*

Clindamycin cream can weaken condoms and contraceptive diaphragms; do not use these products within 72 hours of treatment [102]. Advise women to refrain from sexual activity or to use condoms consistently and correctly during treatment. Douching may increase the risk for relapse and should be discouraged [4].

EVIDENCE-BASED PRACTICE RECOMMENDATION

According to the Centers for Disease Control and Prevention (CDC), patients should be advised to refrain from sexual activity or to use condoms consistently and correctly during the bacterial vaginosis treatment regimen. Patients should also be advised that clindamycin cream is oil based and might weaken latex condoms and diaphragms for five days after use.

(https://www.cdc.gov/std/treatment-guidelines/bv.htm. Last accessed April 24, 2023.)

Level of Evidence: Expert Opinion/Consensus Statement

Intravaginal lactobacillus formulations or probiotics have not shown consistent efficacy as bacterial vaginosis treatment, and no recommendations can be made on their use. Ongoing research will determine their role in bacterial vaginosis treatment and prevention [4; 102].

Persistent or Recurrent Bacterial Vaginosis

Persistent or recurrent bacterial vaginosis is common. Metronidazole gel can reduce the incidence of multiple recurrences, but efficacy may be lost when treatment is discontinued [111]. A sequential approach is suggested, with daily oral metronidazole or tinidazole, followed by daily intravaginal boric acid, and then suppressive long-term metronidazole gel [112]. Suppressive therapy with monthly oral metronidazole plus oral fluconazole can reduce bacterial vaginosis incidence and promote colonization with normal vaginal flora [113]. Persons with HIV infection have greater recurrence rates of bacterial vaginosis [114].

Allergy and Intolerance

With allergy or intolerance to metronidazole or tinidazole, intravaginal clindamycin cream is preferred. Intravaginal metronidazole gel is helpful for those who lack allergy but do not tolerate oral metronidazole [4].

During Pregnancy

Treatment is recommended for all symptomatic pregnant women. Tinidazole should be avoided, but vaginal clindamycin is safe for pregnant women [115]. Treat symptomatic pregnant women with oral or vaginal metronidazole or clindamycin regimens used for nonpregnant women [116].

EPIDIDYMITIS

Acute epididymitis is inflammation of the epididymis with an acute onset of unilateral testicular pain and swelling, often with tenderness of the epididymis and vas deferens, and occasionally with erythema and edema of the overlying skin. Testis involvement is termed epididymo-orchitis. Sexually transmitted acute epididymitis usually is accompanied by urethritis, typically asymptomatic [117]. Clinicians should be vigilant for non-infectious testicular (spermatic cord) torsion in men who present with a sudden onset of symptoms associated with epididymitis, as this condition is a surgical emergency [117].

In sexually active men, *C. trachomatis*, *N. gonorrhoeae*, or *M. genitalium* infection accounts for most cases of acute epididymitis caused by STI. Acute epididymitis caused by sexually transmitted enteric organisms such as *Escherichia coli* may be encountered in MSM. Acute epididymitis unrelated to sexual activity is uncommon in younger patients, and management should involve urologist consultation [117].

CLINICAL FEATURES

Men with acute epididymitis typically present with unilateral testicular pain and tenderness combined with palpable swelling of the epididymis. Inflammation and swelling begin in the tail of the epididymis, followed by extension along the epididymis and testicular swelling. In chronic epididymitis, symptoms of discomfort and/or pain in the scrotum, testicle, or epididymis persist for six or more weeks and are frequently associated with a granulomatous reaction. *Mycobacterium tuberculosis* is the most common granulomatous disease affecting the epididymis and should be suspected in men with past or recent tuberculosis exposure [118].

DIAGNOSIS

If diagnosis is questionable, consult a specialist immediately, because testicular viability may be compromised by testicular torsion [117]. Bilateral symptoms suggest non-infectious cause of testicular pain, and epididymitis should be differentiated from testicular torsion using radionuclide scanning of the scrotum. Ultrasound does not reliably distinguish partial spermatic cord torsion from epididymitis [4].

All cases of suspected acute epididymitis should be evaluated for objective evidence of inflammation by one of the following point-of-care tests [4]:

- Gram or methylene blue/gentian violet stain of urethral secretions
- Positive leukocyte esterase test on first-void urine

TREATMENT OF ACUTE EPIDIDYMITIS	
Likely Cause	**Recommended Treatment**
Sexually transmitted chlamydia or gonorrhea	Ceftriaxone 500 mg IM in a single dose, plus doxycycline 100 mg orally twice per day for 10 days
Enteric organisms only	Levofloxacin 500 mg orally daily for 10 days
Sexually transmitted chlamydia, gonorrhea, or enteric organisms in MSM	Ceftriaxone 500 mg IM in a single dose, plus levofloxacin 500 mg orally once per day for 10 days
Source: [4]	*Table 8*

- Microscopic examination of sediment from first-void urine

The diagnosis should be confirmed by testing for *C. trachomatis* and *N. gonorrhoeae* by NAAT [27].

TREATMENT

To prevent STI complications and transmission, presumptive therapy should be provided during the office visit before all laboratory test results are known. Presumptive treatment selection is based on risk for chlamydia, gonorrhea, and/or enteric organisms (***Table* 8**). Treatment does not differ in men with HIV infection. Effective treatment can provide microbiologic cure, alleviate symptoms, prevent transmission of chlamydia and gonorrhea, and reduce potential chlamydial/gonorrheal epididymitis complications (e.g., infertility, chronic pain) [118; 119; 120].

Hospitalization is required when severe pain or fever suggests torsion, testicular infarction, abscess, or necrotizing fasciitis, or when antimicrobial adherence is unlikely. High fever is uncommon and indicates a complicated infection with hospitalization needed for further evaluation [118; 119; 120].

Use levofloxacin or ofloxacin when infection by enteric organisms is suspected after ruling out gonorrhea, post-prostate biopsy, vasectomy, and other urinary-tract procedures. Bed rest, scrotal elevation, and NSAIDs are recommended until fever and local inflammation subside. Complete resolution of discomfort might not occur until a few weeks after completion of the antibiotic regimen [118; 119; 120]. Treatment of patients with a history of penicillin allergy relies on desensitization; alternative regimens have not been studied [4].

FOLLOW-UP

With acute epididymitis caused by *N. gonorrhoeae* or *C. trachomatis*, advise patients to abstain from sexual intercourse until they and their partners have been adequately treated and symptoms resolved. Instruct patients to return if swelling and tenderness fail to improve by 72 hours of treatment initiation, because re-evaluation of diagnosis and therapy is required. Alternative diagnoses include tumor, abscess, infarction, testicular cancer, tuberculosis, and fungal epididymitis [118; 119; 120].

Management of Sex Partners

In men diagnosed with acute sexually transmitted epididymitis from chlamydial or gonorrheal infection, all sex partners within 60 days of symptom onset should be referred for evaluation, testing, and presumptive treatment. If the last sexual contact was more than 60 days previous, the most recent sex partner should be treated. Female partners should be linked to care; arrange expedited partner therapy and enhanced referral if delay is expected [121; 122].

RARE AND EMERGING BACTERIAL STIs

Chancroid and granuloma inguinale are bacterial STIs that are now rarely encountered in the United States. However, both could be reintroduced by an index case returning from travel to high-prevalence regions such as southeast Asia and Africa; local introduction by sex trafficking of women or men from highly prevalent regions should also be considered [123].

TREATMENT OF CHANCROID INFECTIONS
Any of the following: • Azithromycin 1 g oral, single-dose • Ceftriaxone 250 mg IM, single-dose • Ciprofloxacin 500 mg oral, twice daily for three days • Erythromycin base 500 mg oral, three times per day for seven days
Source: [4] *Table 9*

CHANCROID

Chancroid is an STI characterized by painful genital ulceration and inflammatory inguinal adenopathy caused by infection with *Haemophilus ducreyi* [1]. Chancroid has been widespread in areas of the world where STI control is inadequate, often transmitted by female sex workers with little access to care. Chancroid can only be transmitted when ulceration is present [124]. The importance of chancroid as an STI became elevated in the 1980s when its role in HIV transmission was apparent; risk of HIV transmission increases by 10- to 50-fold from sexual exposure to a person with *H. ducreyi* and HIV co-infection [124].

Chancroid has declined substantially in the United States, with three reported cases in 2018. The CDC states this probably reflects a decline in incidence, but considering the difficulty in culturing *H. ducreyi*, chancroid may also be substantially underdiagnosed [1].

Clinical Features

Following exposure, a papule develops and rapidly progresses to one or more pustular lesions, which rupture to form painful, purulent, shallow ulcers with a granulomatous base that bleeds readily. Multiple ulcers are common, particularly in women. Around 30% of patients develop painful inguinal lymphadenitis that may suppurate, become fluctuant, and spontaneously rupture. Spread beyond the genital tract is rare. Lesions tend to appear in the following sites [124]:

- Men: The prepuce, coronal sulcus, and shaft of the penis
- Women: The external genitalia, rarely in the vagina or on the cervix

Diagnosis

Diagnosis should first rule out other causes of genital ulcer disease. Definitive diagnosis of chancroid requires identification of *H. ducreyi* on special culture media not widely available from commercial sources. Painful genital ulcer with tender suppurative inguinal adenopathy suggests a diagnosis of chancroid [123; 125]. Probable diagnosis of chancroid can be made if all four of the following criteria are met:

- One or more painful genital ulcers
- The clinical presentation
- Dark-field or serologic examination, at least seven days after ulcer onset, negative for *T. pallidum* or syphilis
- PCR or culture test of ulcer exudate negative for herpes simplex virus

Treatment

Successful chancroid treatment cures the infection, resolves clinical symptoms, and prevents transmission. Advanced chancroid can result in scarring despite successful therapy. Ciprofloxacin has a cure rate of more than 90%, and azithromycin or ceftriaxone have advantages as single-dose therapy (***Table 9***). Chancroid culture is not routinely performed, which limits the information available on the current prevalence of antimicrobial resistance in the United States [4; 126; 127].

Uncircumcised men and patients with HIV are less responsive to treatment than circumcised or HIV-negative patients, and HIV testing should be performed when chancroid is diagnosed. Patients should be tested for HIV at the time chancroid is diagnosed. If the initial HIV test results were negative, the provider can consider the benefits of

offering more frequent testing and HIV prophylaxis therapy to persons at increased risk for HIV infection [4].

Treatment During Pregnancy

Ciprofloxacin has low risk to the fetus during pregnancy but is potentially toxic during breastfeeding; alternate drugs should be used during pregnancy and lactation [46]. No adverse effects on pregnancy outcomes from chancroid have been reported [4].

Follow-Up

Re-examine patients three to seven days after starting therapy. Ulcer symptoms usually improve by three days and objectively by seven days after successful therapy. Without improvement, clinicians should consider differential diagnosis, patient co-infection with another STI or HIV, treatment non-adherence, or an antimicrobial-resistant strain of *H. ducrey*i. Time to complete healing depends on ulcer size and location; large ulcers can require more than two weeks, and healing is slower in uncircumcised men with ulcers under the foreskin [4]. Patients with fluctuant buboes will experience symptomatic relief from drainage by needle aspiration, which may need to be repeated [123].

Management of Sex Partners

Even with symptom absence, sex partners should be examined and treated if they had sexual contact with the patients with chancroid in the 10 days preceding symptom onset [4].

GRANULOMA INGUINALE (DONOVANOSIS)

Granuloma inguinale is a rare, progressive infection of genital and perineal skin caused by *Klebsiella* (formerly *Calymmatobacterium*) *granulomatis*, a gram-negative bacterium. The disease is rare in the United States, but endemic in some tropical and developing regions such as India, New Guinea, the Caribbean, central Australia, and southern Africa [128].

Clinical Features

Granuloma inguinale is characterized by slowly progressive, painless, red, raised, and ulcerated skin lesions. Regional lymphadenopathy is uncommon. Common sites of infection include [128; 129]:

- Penis, scrotum, groin, and thighs in men
- Vulva, vagina, and perineum in women
- Anus and buttocks in patients who engage in anal-receptive intercourse
- Face in both sexes

Following a 1- to 12-week incubation, the nodule slowly enlarges, becoming a raised, beefy-red, moist, smooth, foul-smelling lesion. The lesion slowly enlarges, often ulcerates, and may spread to other skin areas. Lesions heal slowly, with scarring. Secondary infections with other bacteria are common and can cause extensive tissue destruction. Occasionally, granuloma inguinale becomes systemic and spreads to the bones, joints, or liver; without treatment, anemia, wasting, and uncommonly death may occur [129; 130].

Diagnosis

Granuloma inguinale is suspected in patients with travel history from endemic areas with characteristic lesions. Diagnosis is confirmed microscopically by the presence of dark-staining Donovan bodies on tissue crush preparation of fluid from scrapings from the edge of lesions. Biopsy specimens are taken if the diagnosis is unclear or if adequate tissue fluid cannot be obtained because lesions are dry, sclerotic, or necrotic. The bacteria do not grow on ordinary culture media [128; 130].

Treatment

A limited number of studies suggest several antimicrobial regimens are effective for the treatment of granuloma inguinale (***Table 10***) [129]. Treatment can halt the progression of lesions. Healing typically proceeds inward from the ulcer margins, and prolonged therapy is usually required to permit granulation and re-epithelialization of ulcers. Relapse can occur 6 to 18 months after an apparently curative therapy response [4]. All patients should be followed until signs and symptoms have resolved.

TREATMENT OF GRANULOMA INGUINALE[a]	
Recommended Regimen	**Alternative Regimens**
Azithromycin 1 g oral once weekly or 500 mg daily	Any of the following: • Doxycycline 100 mg oral twice daily • Erythromycin base 500 mg oral four times per day • One double-strength trimethoprim-sulfamethoxazole (160 mg/800 mg) tablet oral twice daily
[a]All regimens should continue for at least three weeks or until complete healing of all lesions.	
Source: [4]	*Table 10*

MYCOPLASMA GENITALIUM

First identified in the early 1980s, *Mycoplasma genitalium* causes nongonococcal urethritis in men. It is detected in 10% to 30% of men presenting with nonchlamydial nongonococcal urethritis and up to 40% with chronic nongonococcal urethritis [131]. The recent emergence and spread of *M. genitalium* are concerning because of increasing antimicrobial resistance to macrolides, the preferred mode of antibiotic treatment. The penicillins, cephalosporins, and other beta-lactam antibiotics disrupt bacterial cell wall synthesis and are ineffective against *M. genitalium*, which lacks a cell wall [132]. The prevalence of resistance to oral single-dose azithromycin 1 g (the common first-line treatment of urogenital *M. genitalium*) ranges from 44% to 90% in the United States, Canada, and Western Europe [4; 131].

Despite growing concern over *M. genitalium*, there is little known of the long-term clinical consequences of infection. *M. genitalium* colonization/infection in men is associated with a 5.5-fold increased risk of nongonococcal urethritis. In women, *M. genitalium* has been linked to cervicitis, endometritis, PID, infertility, HIV, and adverse birth outcomes. The prevalence of *M. genitalium* in the United States among women is around 1%, compared with *N. gonorrhoeae* (0.4%) and *C. trachomatis* (3%). In contrast to previous contradictory findings associating *M. genitalium* and female genital tract pathology, more recent studies have confirmed this association. For example, 33% to 50% of PID cases are associated with *N. gonorrhoeae* and/or *C. trachomatis*, but many cases have unidentified etiology. Advances in detecting *M. genitalium* by NAAT are raising concerns that *M. genitalium* may play an important pathogenic role in cases in which other STIs are not identified. This issue is further complicated by several studies identifying *M. genitalium* treatment resistance among infected women [133].

Diagnosis

Mycoplasma genitalium is a slow-growing organism. Culture can take up to six months, and few laboratories are able to recover clinical isolates. NAAT for *M. genitalium* is FDA-cleared for use with urethral, penile meatal, endocervical, and vaginal swab specimens [4]. More recently available is a diagnostic test using analyte-specific reagents to target *M. genitalium*. Any lab that performs in-house validation of the assay can use it for *M. genitalium* testing [134].

Treatment

CDC guidelines recommend two-stage therapy approaches, using resistance-guided therapy when macrolide-resistance testing is available. Resistance-guided therapy has reported cure rates >90% [4]. In this approach, doxycycline, 100 mg twice daily for seven days is administered as initial (first-stage) empiric therapy, which reduces bacterial load and facilitates clearance. For patients with macrolide-sensitive *M. genitalium* infection, the second stage consists of high-dose azithromycin 1 gram orally then 500 mg once daily for three days. For those patients with macrolide-resistant infection, the second phase regimen is moxifloxacin 400 mg orally once daily for seven days [4]. If *M. genitalium* is detected by NAAT and resistance testing is not available, recommended treatment is doxycycline, 100 mg two times daily for seven days, followed by moxifloxacin 400 mg once

daily for seven days [4]. When use of moxifloxacin is not feasible, an alternative regimen is initial stage doxycycline followed by azithromycin (1 g orally on day 1 then 500 mg once daily for 7 days) and a clinical test of cure 21 days after completion of therapy.

Recommended PID treatment regimens, which include doxycycline, are not effective against *M. genitalium*. If this organism is detected, and following initial empiric therapy for PID, a regimen of moxifloxacin 400 mg once daily for 14 days has been effective in eradicating the organism [4]. In settings in which *M. genitalium* testing is available, persons with persistent urethritis, cervicitis, or PID accompanied by detection of *M. genitalium* should be treated with moxifloxacin.

Fluoroquinolones other than moxifloxacin are not recommended for the treatment of *M. genitalium*. Microbiologic treatment failure (persistent bacterial detection) ranges from 30% to 67% after levofloxacin and 66% after ofloxacin. In contrast, cure rates for moxifloxacin range from 70% to 100%. The fourth-generation quinolones gatifloxacin and sitafloxacin have somewhat better efficacy against *M. genitalium* than levofloxacin and ofloxacin but are not available in the United States. However, treatment failures have been reported for both the 7- and 10-day moxifloxacin regimens, with few studies evaluating longer duration of treatment [134].

GENERAL MANAGEMENT ISSUES

ANTIMICROBIAL RESISTANCE

Antibiotic-resistant STIs have become a highly concerning issue at both the patient and public health level. The greatest immediate concern is gonorrhea.

Gonorrhea

Over the years, gonorrhea has developed resistance to nearly every drug used to treat it, including sulfonamides, penicillin, tetracycline, and fluoroquinolones. Due to widespread resistance to these antibiotics, by 2007, only cephalosporins—including the oral antibiotic cefixime and the injectable antibiotic ceftriaxone—were left to effectively treat gonorrhea [28; 58].

In 1986, the Gonococcal Isolate Surveillance Project (GISP) was initiated by the CDC to closely monitor how *N. gonorrhoeae* responds to antibiotics. These data are the early warning signs of resistance to recommended treatments. The marker for antibiotic response is the MIC, the lowest concentration of drug needed to stop bacterial growth and an indicator of susceptibility to treatment with a given antibiotic. An increase in MIC over time means greater antibiotic dose levels are required for effective treatment and that resistant strains have appeared and propagated [4; 28; 58].

The epidemiology of antimicrobial resistance has guided decisions about gonococcal treatment recommendations, which have evolved to circumvent changing antimicrobial resistance patterns [4; 28; 58]:

- 1930s: Introduction of sulfonamide antimicrobials to treat gonococcal infection.
- 1940s: Due to increasing resistance, sulfonamides no longer recommended for gonococcal treatment; penicillin becomes treatment of choice.
- 1980s: Due to increasing resistance, penicillin and tetracycline no longer recommended to treat gonococcal infection.
- 1990s: Fluoroquinolones become predominant treatment.
- 2007: Fluoroquinolones no longer recommended with emergence of resistant *N. gonorrhoeae*; cephalosporins (injectable ceftriaxone, oral cefixime) are the only remaining effective antimicrobial class for gonococcal treatment.

- 2012: During 2006–2011, the increasing MIC of cefixime suggested waning effectiveness. Treatment failures with cefixime or other oral cephalosporins were reported in several countries and regions outside the United States. Gonococcal strains with elevated MICs to cefixime were susceptible to azithromycin, and only one regimen, dual treatment with ceftriaxone IM and azithromycin, became recommended for treatment of gonorrhea in the United States.
- 2016: Ceftriaxone IM plus azithromycin remains the only recommended treatment for gonococcal infection.

In 2012, evidence of emerging cefixime resistance led the CDC to issue new guidelines recommending against the use of cefixime in gonorrhea treatment. This change helped slow the emergence of cephalosporin resistance, but the only remaining recommended treatment option for gonorrheal infection is ceftriaxone IM combined with oral azithromycin [28; 58].

This regimen continues to be generally effective, but CDC data indicate that resistance to azithromycin is emerging. During 2013–2014, the percentage of gonorrhea samples with elevated MICs of azithromycin increased by more than 300% (from 0.6% to 2.5%), the largest increase since azithromycin monitoring began. Gonorrhea remains more susceptible to azithromycin than other antibiotics such as penicillin (16.2% with elevated MICs in 2014) or tetracycline (25.3% with elevated MICs in 2014). Azithromycin with ceftriaxone remains effective against gonorrhea, but the data suggest time may be running out [28; 58; 146].

Syphilis

Azithromycin has shown efficacy in the treatment of primary and secondary syphilis. However, *T. pallidum* chromosomal mutations associated with azithromycin resistance and treatment failures have been documented in multiple geographic areas in the United States. Concerns over emerging azithromycin resistance have discouraged its prescribing in STIs other than gonorrhea, except when recommended treatment options are not feasible [4].

FLUOROQUINOLONE ADVERSE EFFECTS

In 2016, the FDA approved labeling changes to systemic fluoroquinolone antibacterial drugs. These drugs became associated with disabling and potentially permanent side effects involving the tendons, muscles, joints, nerves, and CNS. The revised boxed warning—FDA's strongest warning—addresses these serious safety issues. A new warning and update for the patient medication guide was also added [135]. FDA-approved fluoroquinolones include moxifloxacin (Avelox), ciprofloxacin (Cipro), gemifloxacin (Factive), levofloxacin (Levaquin), and ofloxacin.

Fluoroquinolone labels already had a boxed warning for tendinitis, tendon rupture, and worsening of myasthenia gravis, and warnings about risks of peripheral neuropathy, CNS effects, cardiac, dermatologic, and hypersensitivity reactions. In 2013, the FDA added that peripheral neuropathy may be irreversible. Post-marketing reports were submitted to FDA of apparently healthy patients who experienced disabling and potentially permanent side effects involving two or more body systems within hours to weeks after starting the fluoroquinolone, continuing an average of 14 months to as long as nine years after stopping [135].

PENICILLIN ALLERGY

Penicillin is the foundation of antimicrobial treatment for syphilis infection, but some patients have histories of penicillin allergy. The estimated prevalence of penicillin allergy in the United States is 8% to 10%; this may be higher in hospitalized patients [136; 137]. Penicillin allergy imposes a therapeutic quandary, because 10% to 15% of these patients are at risk for an IgE-mediated allergic response to penicillin, with anaphylaxis, bronchospasm, urticaria, or angioedema. Anaphylactic reactions to penicillin can be fatal, and penicillin should be avoided in these patients unless they undergo induction of drug tolerance, termed "desensitization," to temporarily eliminate IgE-mediated hypersensitivity [65; 138; 139; 140].

Many patients with a reported history of penicillin allergy have other types of adverse drug reactions or lose their penicillin sensitivity over time, and in these cases, penicillin can be safely used. Because of the increasing evidence that most persons with documented penicillin allergy do not actually have sensitivity to penicillins and associated beta-lactams, clinicians should make efforts to delabel these patients, if at all possible. Penicillin skin testing with the major and minor determinants of penicillin reliably identifies patients at high risk for IgE-mediated reactions to penicillin [139; 141]. Many tests have used the major determinants only, but without minor determinants, 1% to 10% of patients with true allergy will show false-negative results and risk serious or fatal reactions to penicillin. Patients with a history of severe non-IgE-mediated reactions (e.g., Stevens-Johnson syndrome, toxic epidermal necrolysis, interstitial nephritis, hemolytic anemia) are not candidates for skin testing or challenge and should avoid penicillins indefinitely [141; 142; 143].

Cephalosporin cross-reactivity is another concern with penicillin allergy. Patients with IgE-mediated penicillin allergy history have a 2.5% risk of allergic reaction to first-generation cephalosporins, but negligible risk with most second-generation (cefoxitin) and all third generation (ceftriaxone) cephalosporins [64; 66].

Desensitization

When a candidate for treatment is skin-test positive to one of the penicillin determinants, the patient should be desensitized to penicillin, using a standard desensitization protocol, before proceeding with a specific penicillin regimen. This straightforward, relatively safe procedure can be performed with oral or intravenous penicillin. Oral desensitization is safer and easier to perform. Desensitization should take place in a hospital so serious IgE-mediated allergic reactions, which may occur, are rapidly treated. After the procedure is completed, the first penicillin dose is administered. Following desensitization, penicillin should be maintained continuously for the prescribed duration of the therapy course. After completion of a course of therapy, the desensitization procedure would need to be repeated if penicillin is required in the future [144; 145].

CONCLUSION

Described as hidden epidemics of substantial health and economic consequence, many Americans are reluctant to address STIs because of the biologic and social characteristics of these diseases and associated stigma. However, all communities in the United States are impacted by bacterial STIs. With rising concerns regarding antibiotic resistance and the development of "super strains" of these diseases, identification and appropriate treatment of bacterial STIs is of critical importance. Clinicians have an opportunity to identify patients at risk for bacterial STIs and intervene early in order to limit transmission and debilitating effects of the diseases.

Implicit Bias in Health Care

The role of implicit biases on healthcare outcomes has become a concern, as there is some evidence that implicit biases contribute to health disparities, professionals' attitudes toward and interactions with patients, quality of care, diagnoses, and treatment decisions. This may produce differences in help-seeking, diagnoses, and ultimately treatments and interventions. Implicit biases may also unwittingly produce professional behaviors, attitudes, and interactions that reduce patients' trust and comfort with their provider, leading to earlier termination of visits and/or reduced adherence and follow-up. Disadvantaged groups are marginalized in the healthcare system and vulnerable on multiple levels; health professionals' implicit biases can further exacerbate these existing disadvantages.

Interventions or strategies designed to reduce implicit bias may be categorized as change-based or control-based. Change-based interventions focus on reducing or changing cognitive associations underlying implicit biases. These interventions might include challenging stereotypes. Conversely, control-based interventions involve reducing the effects of the implicit bias on the individual's behaviors. These strategies include increasing awareness of biased thoughts and responses. The two types of interventions are not mutually exclusive and may be used synergistically.

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