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141 Sexually Transmitted Infections: Overview and Clinical Approach

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Sexually Transmitted

Infections: Overview

and Clinical Approach CLASSIFICATION AND EPIDEMIOLOGY Worldwide, most adults acquire at least one sexually transmitted infec tion (STI), and many remain at risk for complications. Each day, for example, more than 1 million STIs are acquired worldwide, placing many affected persons at risk for adverse reproductive health out comes and neoplasia. Certain STIs, such as syphilis, gonorrhea, HIV infection, hepatitis B, and chancroid, often occur in highly intercon nected sexual networks characterized by high rates of partner change or multiple concurrent partners. Such networks, for example, often include persons who engage in transactional sex, some men who have sex with men (MSM), and persons involved in the use of illicit drugs. Other STIs are distributed more evenly throughout populations. For example, chlamydial infections, genital human papillomavirus (HPV) infections, and genital herpes can spread efficiently even in relatively low-risk populations. Finally, modern technologies based on detection of nucleic acid have accelerated elucidation of the role of

sexual trans mission in the spread of some viruses, including Ebola virus and Zika virus, and have provided new evidence of apparent sexual transmission of several bacteria, including group C Neisseria meningitidis and anaer obes associated with bacterial vaginosis (BV). PART 5 Infectious Diseases In general, the product of three factors determines the initial rate of spread of any STI within a population: rate of sexual exposure of sus ceptible to infectious people, efficiency of transmission per exposure, and duration of infectivity of those infected. Accordingly, efforts to prevent and control STIs aim to decrease the rate of sexual exposure of susceptible to infected persons (e.g., through education and efforts to change sexual behavior norms and through control efforts aimed at reducing the proportion of the population infected, including post exposure prophylaxis [PEP]); to decrease the duration of infectivity (through early diagnosis and curative or suppressive treatment); and to decrease the efficiency of transmission (through promotion of condom use and safer sexual practices, use of effective vaccines, and male medi cal circumcision). In all societies, STIs rank among the most common of all infec tious diseases, with at least 40 microorganisms now classified as pre dominantly sexually transmitted or as frequently sexually transmissible (Table 141-1). In developing countries, with three-quarters of the world's population and 90% of the world's STIs, factors such as popu lation growth (especially in adolescent and young-adult age groups), rural-to-urban migration, wars, limited or no provision of reproductive health services for women, and poverty create exceptional vulnerability to disease resulting from unprotected sex. During the 1990s in China, Russia, the other states of the former Soviet Union, and South Africa,

TABLE 141-1 Sexually Transmitted and Sexually Transmissible Microorganisms BACTERIA VIRUSES OTHERa Transmitted in Adults Predominantly by Sexual Intercourse Neisseria gonorrhoeae Chlamydia trachomatis Treponema pallidum Haemophilus ducreyi Klebsiella (Calymmatobacterium) granulomatis Ureaplasma urealyticum Mycoplasma genitalium HIV (types 1 and 2) Human T-cell lymphotropic virus type 1 Herpes simplex virus type 2 Human papillomavirus (multiple genital genotypes) Hepatitis B virusb Trichomonas vaginalis Pthirus pubis Molluscum contagiosum virus Sexual Transmission Repeatedly Described but Not Well Defined or Not the Predominant Mode Mycoplasma hominis Gardnerella vaginalis and other vaginal bacteria Group B Streptococcus Mobiluncus spp. Helicobacter cinaedi Helicobacter fennelliae Anaerobes associated with bacterial vaginosis Leptotrichia/Sneathia Group C Neisseria meningitidis Cytomegalovirus Human T-cell lymphotropic virus type 2 Hepatitis C virus (?) Hepatitis D virus Herpes simplex virus type 1 Zika virus Ebola virus (?) Epstein-Barr virus Human herpesvirus type 8 Candida albicans Sarcoptes scabiei Transmitted by Sexual Contact Involving Oral–Fecal Exposure; of Declining Importance in Men Who Have Sex with Men Shigella spp. Campylobacter spp. Hepatitis A virus Giardia lamblia Entamoeba histolytica aIncludes protozoa, ectoparasites, and fungi. bAmong U.S. patients for whom a risk factor can be ascertained, most hepatitis B virus infections are transmitted sexually. internal social structures changed rapidly as borders opened to the West, unleashing enormous new epidemics of HIV infection and other STIs; such patterns persist in the face of ongoing conflicts. Despite advances in the provision of highly effective antiretroviral therapy worldwide, HIV remains the leading cause of death in some develop ing countries, and HPV and hepatitis B virus (HBV) remain important causes of cervical and hepatocellular carcinoma, respectively—two of the most common (and preventable) malignancies in the developing world. Sexually transmitted herpes simplex virus (HSV) infection causes most genital ulcer disease throughout the world, and an increas ing proportion of cases of genital herpes occur in developing countries with generalized HIV epidemics, where the positive feedback loop between HSV and HIV

transmission remains intractable. Despite this consistent link, randomized trials evaluating the efficacy of antiviral therapy in suppressing HSV in both HIV-uninfected and HIV-infected persons have demonstrated no protective effect against acquisition or transmission of HIV. The World Health Organization estimated that 357 million new cases of four curable STIs—gonorrhea, chlamydial infection, syphilis, and trichomoniasis—occurred annually in recent years. Up to 50% of women of reproductive age in developing countries have BV (arguably acquired sexually). All of these curable STIs have been associated with increased risk of HIV transmission or acquisition. In the United States, the prevalence of antibody to HSV-2 began to fall in the late 1990s, especially among adolescents and young adults; the decline was presumably due to delayed sexual debut, increased condom use, and lower rates of multiple (four or more) sex partners— all well documented by the U.S. Youth Risk Behavior Surveillance System. The estimated annual incidence of HBV infection has also declined dramatically since the mid-1980s; this decrease is probably attributable to now-widespread administration of hepatitis B vaccine in infancy. Genital HPV remains the most common sexually transmit ted pathogen in the United States, infecting 60% of a cohort of initially

HPV-negative, sexually active Washington state college women within 5 years in a study conducted from 1990 to 2000—i.e., during the pre–HPV immunization era. Global expansion of HPV vaccine cover age among young women has already shown promise in reducing the incidence of infection with the HPV types included in the vaccines and of conditions associated with these viruses, including invasive cervical cancer; however, gaps in immunization coverage remain. In industrialized countries, fear of HIV infection in the mid-1980s and through the mid-2000s, coupled with widespread behavioral interventions and better-organized systems of care for the curable STIs, initially helped curb the transmission of several STDs. However, with current antiretroviral therapy, HIV has become for many a chronic disease associated with a normal life span and high quality of life, and HIV pre-exposure prophylaxis (PrEP) has proven highly effective in preventing HIV acquisition, further reducing motivation to use barrier protection such as condoms. Rates of gonorrhea and syphilis remain higher in the United States than in any other Western industrialized country. In the United States, the Centers for Disease Control and Prevention (CDC) has compiled reported rates of STIs since 1941. The incidence of reported gonorrhea peaked at 468 cases per 100,000 population in the mid-1970s and fell to a low of 98 cases per 100,000 in 2012; in 2018, the case rate was 179.1 per 100,000 persons, which is more than an 80% increase since 2009 when the number of new cases reached an all-time low. With increased testing and more sensitive tests, the incidence of reported Chlamydia trachomatis infection has been increasing steadily since reporting began in 1984, reaching an all-time peak of 457.6 cases per 100,000 in 2011. The incidence of primary and secondary syphilis per 100,000 peaked at 71 cases in 1946, fell rapidly to 3.9 cases in 1956, ranged from ~10 to 15 cases through 1987 (with markedly increased rates among MSM and African Americans), and then fell to a nadir of 2.1 cases in 2000–2001 (with rates falling most rapidly among hetero sexual African Americans). However, since 1996, with the introduc tion of highly active antiretroviral therapy, gonorrhea, syphilis, and chlamydial infection have had a remarkable resurgence among MSM in North America and Europe, where outbreaks of a rare type of chla mydial infection (lymphogranuloma venereum [LGV]) that had virtu ally disappeared during the AIDS era have occurred. In 2022, 207,255 cases of syphilis (all stages and congenital syphilis) were reported in the United States, which is the greatest number of cases reported since 1950 and an increase of 17.3% since 2021. In 2022, 45% of primary and secondary syphilis cases among males reported to the CDC were in MSM, but incidence has also increased in

women, with a concomitant increase in congenital syphilis. In 2022, 3755 cases of congenital syphi lis were reported, including 282 congenital syphilis-related stillbirths and infant deaths. The national congenital syphilis rate of 102.5 cases per 100,000 live births in 2022 represents a 30.6% increase relative to 2021 and is the highest reported rate since 1991. Moreover, the uptake of oral PrEP for HIV-1 acquisition has increased among MSM since its initial approval for this purpose in 2012 and has been associated with reports of reduced condom-use frequency and concomitantly increased STI acquisition. These devel opments have resulted in a soaring incidence of STIs, with increas ing co-infection with HIV and other sexually transmitted pathogens (particularly Treponema pallidum, the cause of syphilis; and Neisseria gonorrhoeae, the cause of gonorrhea), primarily among MSM. MANAGEMENT OF COMMON SEXUALLY TRANSMITTED DISEASE SYNDROMES Although other chapters discuss management of specific STIs, most patients are managed (at least initially) on the basis of presenting symptoms and signs and associated risk factors, even in industrialized countries. Table 141-2 lists some of the most common clinical sexually transmitted disease (STD) syndromes and their microbial etiologies. Strategies for their management are outlined below. Chapters 207 and 208 address the management of infections with human retroviruses. STD care and management begin with risk assessment and proceed to clinical assessment, diagnostic testing or screening, treatment, and prevention. Risk assessment guides detection and interpretation of

TABLE 141-2 Major Sexually Transmitted Disease Syndromes and Sexually Transmitted Microbial Etiologies SEXUALLY TRANSMITTED MICROBIAL ETIOLOGIES SYNDROME AIDS HIV types 1 and 2 Urethritis: males Neisseria gonorrhoeae, Chlamydia trachomatis, Mycoplasma genitalium, Ureaplasma urealyticum (subspecies urealyticum), Trichomonas vaginalis, HSV, some anaerobic bacteria, Leptotrichia/Sneathia Epididymitis C. trachomatis, N. gonorrhoeae, and (in older men or men who have sex with men) coliform bacteria Lower genital tract infections: females Cystitis/urethritis C. trachomatis, N. gonorrhoeae, HSV Mucopurulent cervicitis C. trachomatis, N. gonorrhoeae, M. genitalium Vulvitis Candida albicans, HSV Bartholinitis C. albicans, T. vaginalis Vulvovaginitis C. albicans, T. vaginalis BV BV-associated bacteria (see text) Acute pelvic inflammatory disease N. gonorrhoeae, C. trachomatis, BV-associated bacteria, M. genitalium, group B streptococci Infertility N. gonorrhoeae, C. trachomatis, BV-associated bacteria Ulcerative lesions of the genitalia HSV-1, HSV-2, Treponema pallidum, Haemophilus ducreyi, C. trachomatis (LGV strains), Klebsiella (Calymmatobacterium) granulomatis CHAPTER 141 Complications of pregnancy/ puerperium Several pathogens implicated Intestinal infections Proctitis C. trachomatis, N. gonorrhoeae, HSV,

Proctocolitis or enterocolitis Campylobacter spp., Shigella spp., Entamoeba histolytica, Helicobacter spp., other enteric pathogens Enteritis Giardia lamblia Acute arthritis with urogenital infection or viremia N. gonorrhoeae (e.g., DGI), C. trachomatis

(e.g., reactive arthritis), HBV Genital and anal warts HPV (30 genital types) Mononucleosis syndrome CMV, HIV, EBV Hepatitis Hepatitis viruses, T. pallidum, CMV, EBV Neoplasias Squamous cell dysplasias HPV (especially types 16, 18, 31, 45) and cancers of the cervix, anus, vulva, vagina, or penis Kaposi’s sarcoma, bodyHHV-8 cavity lymphomas T-cell leukemia HTLV-1 Hepatocellular carcinoma HBV Tropical spastic paraparesis HTLV-1 Scabies Sarcoptes scabiei Pubic lice Pthirus pubis Abbreviations: BV, bacterial vaginosis; CMV, cytomegalovirus; DGI, disseminated gonococcal

infection; EBV, Epstein-Barr virus; HBV, hepatitis B virus; HHV-8, human herpesvirus type 8; HPV, human papillomavirus; HSV, herpes simplex virus; HTLV, human T-cell lymphotropic virus; LGV, lymphogranuloma venereum. symptoms that could denote an STD; decisions on screening or pro phylactic/preventive treatment; risk reduction counseling and inter vention (e.g., hepatitis B vaccination); treatment of partners of patients with known infections; and behavioral risk reduction by the patient. Consideration of routine demographic data (e.g., identified gender, age, area of residence) is a simple first step in this risk assessment. For example, national guidelines strongly recommend routine screening of

TABLE 141-3 Eleven-Question Sexually Transmitted Disease (STD)/ HIV Risk Assessment Framing Statement In order to provide the best care for you today and to understand whether we should consider certain infections, I'd like to talk about your sexual behavior. Screening Questions (1) Do you have any reason to think you might have a sexually transmitted infection? If so, what reason? (2) For all adolescents <18 years old: Have you begun having any kind of sex yet? STD History (3) Have you ever had any sexually transmitted infections or any genital infections? If so, which ones? Sexual Preference (4) Have you had sex with men, women, or both? Injection Drug Use (5) Have you ever injected yourself with drugs? (If yes, have you ever shared needles or injection equipment?) (6) Have you ever had sex with anyone who had ever injected drugs? Characteristics of Partner(s) (7) Have any of your sex partners had any sexually transmitted infections? If so, which ones? (8) Have any of your sex partners had other sex partners during the time you've been together? STD Symptoms Checklist (9) Have you recently developed any of these symptoms? For Men For Women PART 5 Infectious Diseases (a) Discharge of pus (drip) from the (a) Abnormal vaginal discharge penis (b) Genital sores (ulcers) or rash (increased amount, abnormal odor, abnormal yellow color) (b) Genital sores (ulcers), rash, or itching Sexual Practices, Past 2 Months (for patients answering yes to any of the above questions, to guide examination and testing) (10) Now I'd like to ask what parts of your body may have been sexually exposed to an STD (e.g., your penis, mouth, vagina, anus). Query About Interest in STD Screening Tests (for patients answering no to all of the above questions) (11) Would you like to be tested for HIV or any other STDs today? (If yes, clinician can explore which STD and why.) Source: Adapted from JR Curtis, KK Holmes, in KK Holmes et al (eds): Sexually Transmitted Diseases, 4th ed. New York, McGraw-Hill, 2008. sexually active females ≤25 years of age for C. trachomatis infection. Table 141-3 provides a set of 11 STD/HIV risk-assessment questions that clinicians can pose verbally or that health care systems can adapt (with yes/no responses) into a routine self-administered questionnaire. The initial framing statement gives permission to discuss topics that may be difficult for the patient to disclose. Risk assessment is followed by clinical assessment (elicitation of information on specific current symptoms and signs of STDs). Con firmatory diagnostic tests (for persons with symptoms or signs) or screening tests (for those without symptoms or signs) may involve microscopic examination, culture, nucleic acid amplification tests (NAATs), or serology. Initial syndrome-based treatment should cover the most likely causes. For certain syndromes, results of rapid tests can narrow the spectrum of this initial therapy (e.g., pH of vaginal fluid for women with vaginal discharge, Gram's stain of urethral discharge for men with urethral discharge, rapid plasma reagin test for genital ulcer to assess the probability of syphilis). After the institution of treatment, STD management proceeds to the "4 Cs" of prevention and control: contact tracing (see "Prevention and Control of STIs," below), ensuring compliance with therapy, and counseling on risk reduction, including condom promotion and provision as well as motivational interviewing for risk reduction.

Consistent with current guidelines, all adults should be screened for infection with HIV-1 at least once, and more frequently if they are at elevated risk for acquisition of this infection. ■ ■URETHRITIS IN MEN Urethritis in men produces urethral discharge, dysuria, or both, usually without frequency of urination. Causes include N. gonorrhoeae, C. trachomatis, Mycoplasma genitalium, Ureaplasma urealyticum, Tricho monas vaginalis, HSV, and (rarely) adenovirus. Until recently, C. trachomatis caused ~30–40% of cases of nongono coccal urethritis (NGU), particularly in heterosexual men; however, the proportion of cases due to this organism has probably declined in some populations served by effective chlamydial control programs, and older men with urethritis appear less likely to have chlamydial infec tion. HSV and T. vaginalis each cause a small proportion of NGU cases in the United States. Recently, multiple studies have consistently impli cated M. genitalium as a probable cause of many Chlamydia-negative cases. Fewer studies than in the past have implicated Ureaplasma; the ureaplasmas have been differentiated into U. urealyticum and Urea plasma parvum, and a few studies suggest that U. urealyticum—but not U. parvum—is associated with NGU; for this reason, neither testing nor presumptive treatment for ureaplasmas in the setting of urethritis is recommended. Coliform bacteria can cause urethritis in men who engage in insertive anal intercourse. More recently, anaerobic bacte ria that are characteristically involved in BV, especially Leptotrichia/ Sneathia species, have occasionally been associated with urethritis in heterosexual men. Recommendations for the initial diagnosis of ure thritis in men currently include specific tests only for N. gonorrhoeae and C. trachomatis; they do not yet include testing for M. genitalium, although a NAAT is now commercially available for the latter. APPROACH TO THE PATIENT Urethritis in Men The following summarizes the approach to the male patient with suspected urethritis:

1. Establish the presence of urethritis. If proximal-to-distal “milk ing” of the urethra does not express a purulent or mucopurulent discharge, even after the patient has not voided for several hours (or preferably overnight), a Gram’s-stained smear of an anterior urethral specimen obtained by passage of a small urethrogenital swab 2–3 cm into the urethra usually reveals ≥2 neutrophils per 1000× field when urethritis is present; in gonococcal infec tion, such a smear usually reveals gram-negative intracellular diplococci as well. Patients with symptoms who lack objective evidence of urethritis generally do not benefit from repeated courses of antibiotics, and other etiologies of such symptoms may be considered.
2. Evaluate for complications or alternative diagnoses. A brief history and examination can exclude epididymitis and systemic compli cations, such as disseminated gonococcal infection (DGI) and reactive arthritis. Although digital examination of the prostate gland seldom contributes to the evaluation of sexually active young men with urethritis, men with dysuria who lack evidence of urethritis as well as sexually inactive men with urethritis should undergo prostate palpation, urinalysis, and urine culture to exclude bacterial prostatitis and cystitis.
3. Evaluate for gonococcal and chlamydial infection. An absence of typical gram-negative diplococci on Gram’s-stained smear of urethral exudate containing inflammatory cells warrants a preliminary diagnosis of NGU, as this test is 98% sensitive for the diagnosis of gonococcal urethral infection. However, most men with symptoms and/or signs of urethritis are simultaneously assessed for infection with N. gonorrhoeae and C. trachomatis by NAATs of first-catch urine. The urine specimen tested should consist of the first 10–15 mL of the stream, and if possible, patients should not have voided for the prior

2 h. Culture or NAAT for N. gonorrhoeae may yield positive results even when

Gram’s staining is negative; certain strains of N. gonorrhoeae can result in negative urethral Gram’s stains in up to 30% of cases of urethral infection. Results of tests for gonococcal and chlamydial infection predict the patient’s prognosis (with greater risk for recurrent NGU if neither chlamydiae nor gonococci are found than if either is detected) and can guide both the counseling given to the patient and the management of the patient’s sexual partner(s). 4. Treat urethritis promptly while test results are pending. TREATMENT Urethritis in Men Table 141-4 summarizes the steps in management of urethral dis charge and/or dysuria in sexually active men. In practice, if Gram’s stain does not reveal gonococci, urethritis is treated with a regimen effective for NGU, such as azithromycin or doxycycline. Both are generally effective. Although azithromycin has been more effective than doxycycline for M. genitalium infection, the efficacy of azithromycin for treatment of M. genitalium is rapidly declining. Alternatives include moxifloxacin and pristinamycin, a streptogramin antibiotic available in some countries. If gonococci are demonstrated by Gram’s stain or if no diagnostic tests are per formed to exclude gonorrhea definitively, treatment should include parenteral cephalosporin therapy for gonorrhea (Chap. 161). Doxy cycline is the preferred antibiotic for treating C. trachomatis infec tion, which can cause urethral co-infection in men with gonococcal urethritis. Sexual partners with contact to the index patient in the past 60 days should also be tested for gonorrhea and chlamydial infection. Regardless of whether they are tested for these infections, however, they should receive the same regimen given to the index case. Patients with confirmed persistence or recurrence of urethritis after treatment should be re-treated with the initial regimen if they did not comply with the original treatment or were reexposed to an untreated partner. Most persistent urethritis is due to M. genitalium, and prompt diagnostic testing and/or treatment for M. genitalium is recommended. TABLE 141-4 Management of Urethral Discharge in Men USUAL CAUSES USUAL INITIAL EVALUATION Chlamydia trachomatis Neisseria gonorrhoeae Mycoplasma genitalium Ureaplasma urealyticum Trichomonas vaginalis Herpes simplex virus Demonstration of urethral discharge or pyuria Exclusion of local or systemic complications Urethral Gram’s stain to confirm urethritis, detect gram-negative diplococci Test for N. gonorrhoeae, C. trachomatis,

M. genitalium (if indicated and available) Initial Treatment for Patient and Partners Treat gonorrhea (unless excluded): Ceftriaxone (500 mg IMa) For persons weighing ≥150 kg, 1 gram of ceftriaxone IM should be administered Management of Recurrence Confirm objective evidence of urethritis. If patient was reexposed to untreated or new partner, repeat treatment of patient and partner. If patient was not reexposed, consider infection with T. vaginalisb or antibioticresistant M. genitaliumc, and treat accordingly (metronidazole for trichomoniasis; azithromycin for M. genitalium followed by moxifloxacin if needed). aNeither oral cephalosporins nor fluoroquinolones are recommended for treatment of gonorrhea in the United States because of the emergence of increasing fluoroquinolone resistance in N. gonorrhoeae, especially (but not only) among men who have sex with men, and the decreasing susceptibility of a small proportion of gonococci to ceftriaxone (Fig. 136-1). Updates on the emergence of antimicrobial resistance in N. gonorrhoeae can be obtained from the Centers for Disease Control and Prevention at http://www.cdc.gov/std. bIn men, the diagnosis of T. vaginalis infection requires nucleic acid amplification testing of a urethral swab specimen obtained before voiding. cM. genitalium is often resistant to doxycycline and azithromycin but is usually susceptible to the fluoroquinolone moxifloxacin. Moxifloxacin can be considered for treatment of refractory nongonococcal, nonchlamydial urethritis.

National and international guidelines exist for treatment of gonococcal urethritis, typically with ceftriaxone. However, con sensus is still lacking on treatment of urethritis that persists after treatment and cure of gonorrhea. Ideally, the approach would involve testing for potential causes of persistent urethritis (e.g., M. genitalium) and antimicrobial susceptibility testing in settings and populations where antimicrobial resistance is emerging. Currently, assays are available that can detect M. genitalium, and some experts believe it is time to integrate such testing into STD care. If M. genitalium is detected, the persistent urethritis can be treated with azithromycin or moxifloxacin in light of local patterns of antimi crobial susceptibility.

In heterosexual men with a high likelihood of exposure to tricho moniasis, an intraurethral swab specimen and a first-voided urine sample should be tested for T. vaginalis using NAAT. Presumptive treatment with metronidazole or tinidazole (2 g by mouth in a single dose) should be given. For MSM, trichomoniasis is unlikely, and consideration of a course of moxifloxacin is warranted. Because MSM also have the highest prevalence rates of antimicrobialresistant N. gonorrhoeae, this possibility, even if apparently ruled out at the initial presentation, should be kept in mind. ■ ■EPIDIDYMITIS Acute epididymitis, almost always unilateral, produces pain, swelling, and tenderness of the epididymis, with or without symptoms or signs of urethritis. This condition must be differentiated from testicular tor sion, tumor, and trauma. Torsion, a surgical emergency, usually occurs in the second or third decade of life and produces a sudden onset of pain, elevation of the testicle within the scrotal sac, rotation of the epi didymis from a posterior to an anterior position, and absence of blood flow on Doppler ultrasound. Persistence of symptoms after a course of therapy for epididymitis suggests the possibility of testicular tumor or of a chronic granulomatous disease, such as tuberculosis. In sexually active men under age 35, acute epididymitis is caused most frequently by C. trachomatis and less commonly by N. gonorrhoeae and is usu ally associated with overt or subclinical urethritis. Acute epididymitis occurring in older men or following urinary tract instrumentation is usually caused by urinary pathogens. These older men usually have no urethritis but do have bacteriuria. Similarly, epididymitis in MSM who have practiced insertive rectal intercourse is often caused by Enterobacteriaceae. CHAPTER 141 Sexually Transmitted Infections: Overview and Clinical Approach
TREATMENT Epididymitis Ceftriaxone (500 mg as a single dose IM) followed by doxycycline (100 mg by mouth twice daily for 10 days) constitutes effective treat ment for epididymitis caused by N. gonorrhoeae or C. trachomatis. Nei ther oral cephalosporins nor fluoroquinolones are recommended for treatment of gonorrhea in the United States because of resis tance in N. gonorrhoeae, especially (but not only) among MSM (Fig. 141-1). Given rapidly escalating rates of resistance in N. gonor rhoeae to azithromycin, this antibiotic is no longer recommended as co-therapy with a parenteral ceftriaxone for gonorrhea. When infection with Enterobacteriaceae is suspected, oral levofloxacin (500 mg once daily for 10 days) added to parenteral ceftriaxone (500 mg IM once) is effective for syndrome-based initial treatment. ■ ■URETHRITIS AND THE URETHRAL

SYNDROME IN WOMEN C. trachomatis, N. gonorrhoeae, and occasionally HSV cause symp tomatic urethritis—known as the urethral syndrome in women—that is characterized by “internal” dysuria (usually without urinary urgency or frequency), pyuria, and an absence of Escherichia coli and other uropathogens at counts of ≥102/mL in urine. In contrast, the dysuria associated with vulvar herpes or vulvovaginal candidiasis (and perhaps with trichomoniasis) is often described as “external,” being caused

40% 30% Percentage 20% 10% 0%

Antimicrobials

n (%)

n (%)

n (%)

n (%)

n (%)

n (%)

n (%)

n (%)

n (%)

n (%)

n (%) Azithromycin

(0.3)

(0.3)

(0.6)

(0.4)

(0.9)

(0.6)

(0.2)

(0.4)

(0.2)

(0.2)

(0.5) Cefixime

(0.2)

(0.2)

(0.2)

(0.1)

(0.1)

(0.1)

(0.1) N/A N/A

(0.8)

(1.4) Ceftriaxone

(0.1)

(0.3)

(0.1)

(0.0)

(0.1)

(0.1)

(0.0)

(0.1)

(0.1)

(0.3)

(0.3) Ciprofloxacin

(0.3)

(0.7)

(2.2)

(4.1)

(6.8)

(9.4)

(13.8)

(14.8)

(13.5)

(9.6)

(12.5) Penicillin

(14.2)

(11.4)

(8.2)

(6.6)

(6.5)

(9.4)

(11.5)

(12.9)

(11.2)

(12.5)

(12.9) Tetracycline

(19.9)

(17.0)

(15.2)

(14.4)

(14.4)

(17.3)

(20.6)

(20.5)

(18.2)

(16.7)

(20.2) PART 5 Infectious Diseases Antimicrobials

n (%)

n (%)

n (%)

n (%)

n (%)

n (%)

n (%)

n (%)

n (%)

n (%)

n (%) Azithromycin

(0.3)

(0.3)

(0.6)

(2.5)

(2.6)

(3.6)

(4.4)

(4.6)

(5.1)

(5.8)

(4.6) Cefixime

(1.4)

(0.9)

(0.4)

(0.7)

(0.5)

(0.3)

(0.4)

(0.3)

(0.3)

(0.3)

(0.2) Ceftriaxone

(0.4)

(0.3)

(0.1)

(0.1)

(0.3)

(0.3)

(0.2)

(0.2)

(0.1)

(0.1)

(0.1) Ciprofloxacin

(13.3)

(14.7)

(16.1)

(19.2)

(22.3)

(26.8)

(30.1)

(31.2)

(35.4)

(34.8)

(32.8) Penicillin

(11.8)

(13.2)

(12.2)

(16.2)

(15.7)

(17.8)

(15.8)

(13.7)

(12.8)

(12.3)

(12.0) Tetracycline

(22.8)

(23.4)

(23.7)

(25.3)

(24.2)

(22.6)

(23.1)

(25.6)

(27.8)

(19.7)

(20.6) FIGURE 141-1 Percentage of Tetracycline, Penicillin, or Ciprofloxacin Resistance* or Elevated Cefixime, Ceftriaxone, or Azithromycin Minimum Inhibitory Concentrations (MICs)† by Year, Gonococcal Isolate Surveillance Project (GISP), 2001-2022. *Resistance: ciprofloxacin MIC ≥1.0 µg/mL; penicillin MIC ≥2.0 µg/mL or b-lactamase positive; tetracycline MIC ≥2.0 µg/mL. †Elevated MICs: azithromycin MIC ≥1.0 µg/mL (2000–2004), MIC ≥2.0 µg/mL (2005–2022); ceftriaxone MIC ≥0.125 µg/mL; cefixime MIC ≥0.25 µg/mL. Cefixime susceptibility was not tested in 2007 and 2008. by painful contact of urine with the inflamed or ulcerated labia or introitus. Acute onset, association with urinary urgency or frequency, hematuria, or suprapubic bladder tenderness suggests bacterial cystitis. Among women with symptoms of acute bacterial cystitis, costoverte bral pain and tenderness or fever suggest acute pyelonephritis. The management of bacterial urinary tract infection (UTI) is discussed in Chap. 140. Signs of vulvovaginitis, coupled with symptoms of external dysuria, suggest vulvar infection (e.g., with HSV or Candida albicans). Among dysuric women without signs of vulvovaginitis, bacterial UTI must be differentiated from the urethral syndrome by assessment of risk, evalu ation of the pattern of symptoms and signs, and specific microbiologic

Ciprofloxacin Tetracycline Penicillin Azithromycin Cefixime Ceftriaxone

Year testing. An STI etiology of the urethral syndrome is suggested by young age, more than one current sexual partner, a new partner within the past month, a partner with urethritis, or coexisting mucopurulent cer vicitis (see below). The finding of a single urinary pathogen, such as E. coli or Staphylococcus saprophyticus, at a concentration of ≥102/mL in a properly collected specimen of midstream urine from a dysuric woman with pyuria indicates probable bacterial UTI, whereas pyuria with <102 conventional uropathogens per milliliter of urine (“sterile” pyuria) sug gests acute urethral syndrome due to C. trachomatis or N. gonorrhoeae. Gonorrhea and chlamydial infection should be sought by specific tests (e.g., NAATs of vaginal secretions collected with a swab). Among dys uric women with sterile pyuria caused by infection with N. gonorrhoeae

or C. trachomatis, appropriate treatment alleviates dysuria. The role of M. genitalium in the urethral syndrome in women remains undefined. ■ ■VULVOVAGINAL INFECTIONS Abnormal Vaginal Discharge If directly questioned about vagi nal discharge during routine health checkups, many women acknowl edge having nonspecific symptoms of vaginal discharge that do not correlate with objective signs of inflammation or with actual infection. However, unsolicited reporting of abnormal vaginal discharge often denotes BV or trichomoniasis. Specifically, an abnormally increased amount or an abnormal odor of the discharge is associated with one or both of these conditions. Cervical infection with N. gonorrhoeae or C. trachomatis does not often cause an increased amount or abnormal odor of discharge; however, when these pathogens cause cervicitis, they—like T. vaginalis—often result in an increased number of neu trophils in vaginal fluid, which thus takes on a yellow color. Vulvar conditions such as genital herpes or vulvovaginal candidiasis can cause vulvar pruritus, burning, irritation, or lesions as well as external dysuria (as urine passes over the inflamed vulva or areas of epithelial disruption) or vulvar dyspareunia. Certain vulvovaginal infections may have serious sequelae. Tricho moniasis, BV, and vulvovaginal candidiasis have all been associated with increased risk of acquisition of HIV infection; BV promotes HIV transmission from HIV-infected women to their male sex partners. Vaginal trichomoniasis and BV early in pregnancy independently TABLE 141-5 Diagnostic Features and Management of Vaginal Infection NORMAL VAGINAL EXAMINATION VULVOVAGINAL CANDIDIASIS TRICHOMONAL VAGINITIS BACTERIAL VAGINOSIS (BV) FEATURE Etiology Uninfected; lactobacilli predominant Candida albicans Trichomonas vaginalis Associated with Gardnerella vaginalis, various anaerobic bacteria, and mycoplasmas Typical symptoms None Vulvar itching and/or irritation Profuse discharge; vulvar itching Discharge Amount Variable; usually scant Scant Often profuse Moderate Colora Clear or translucent White White or yellow White or gray Consistency Nonhomogeneous, flocculent Clumped; adherent plaques Homogeneous Homogeneous, low viscosity; uniformly coats vaginal walls Inflammation of vulvar or vaginal epithelium None Erythema of vaginal epithelium, introitus; vulvar dermatitis, fissures common pH of vaginal fluidb Usually ≤4.5 Usually ≤4.5 Usually ≥5 Usually >4.5 Amine (“fishy”) odor with 10% KOH None None May be present Present Microscopyc Normal epithelial cells; lactobacilli predominant Leukocytes, epithelial cells; mycelia or pseudomycelia in up to 80% of

C. albicans culture–positive persons with typical symptoms Other laboratory findings Isolation of Candida spp. Isolation of T. vaginalis or positive NAATd Diagnosis of BV by NAATd Usual treatment None Azole cream, tablet, or suppository—e.g., miconazole (100-mg vaginal suppository) or clotrimazole (100-mg vaginal tablet) once daily for 7 days Fluconazole, 150 mg orally (single dose) Usual management of sexual partner None None; topical treatment if candidal dermatitis of penis is detected aColor of discharge is best determined by examination against the white background of a swab. bA pH determination is not useful if blood is present or if the test is performed on endocervical secretions. cTo detect fungal elements, vaginal fluid is digested with 10% KOH prior to microscopic examination; to examine for other features, fluid is mixed (1:1) with physiologic saline. Gram’s stain is also excellent for detecting yeasts (less predictive of vulvovaginitis) and pseudomycelia or mycelia (strongly predictive of vulvovaginitis) and for distinguishing normal flora from the mixed flora seen in bacterial vaginosis, but it is less sensitive than the saline preparation for detection of T. vaginalis. dNAAT, nucleic acid amplification test (where available). NAAT for diagnosis of BV typically tests for combinations of BV-associated bacteria and absence of Lactobacillus species.

predict premature onset of labor. BV can also lead to anaerobic bacte rial infection of the endometrium and salpinges. Vaginitis may be an early and prominent feature of toxic shock syndrome, and recurrent or chronic vulvovaginal candidiasis develops with increased frequency among women who have systemic illnesses, such as diabetes mellitus or HIV-related immunosuppression (although only a very small propor tion of women with recurrent vulvovaginal candidiasis in industrial ized countries actually have a serious predisposing illness).

Thus, vulvovaginal symptoms or signs warrant careful evaluation, including speculum and pelvic examination, diagnostic testing, and appropriate therapy specific for the infection identified. Unfortunately, clinicians do not always perform the tests required to establish the cause of such symptoms. Further, self-diagnosis of a specific type of infection—including vulvovaginal candidiasis—is often incorrect. The diagnosis and treatment of the three most common types of vaginal infection are summarized in Table 141-5. Inspection of the vulva and perineum may reveal tender genital ulcerations or fissures (typically due to HSV infection or vulvovaginal candidiasis) or discharge visible at the introitus before insertion of a speculum (suggestive of BV or trichomoniasis). Speculum examina tion permits the clinician to discern whether the discharge appears abnormal and whether it emanates from the cervical os (mucoid and, if abnormal, yellow) or from the vagina (not mucoid, since the vaginal epithelium does not produce mucus). Symptoms or signs of abnormal vaginal discharge should prompt testing of vaginal fluid for pH, for a fishy odor when mixed with 10% KOH, and for certain microscopic CHAPTER 141 Sexually Transmitted Infections: Overview and Clinical Approach
Malodorous, slightly increased discharge Erythema of vaginal and vulvar epithelium; colpitis macularis None Leukocytes; motile trichomonads seen in 80–90% of symptomatic patients, less often in the absence of symptoms Clue cells; few leukocytes; no lactobacilli or only a few outnumbered by profuse mixed microbiota, nearly always including

G. vaginalis plus anaerobic species on Gram’s stain (Nugent’s score ≥7) Metronidazole or tinidazole,

2 g orally (single dose) Metronidazole, 500 mg PO bid for 7 days Metronidazole, 500 mg PO bid for 7 days Metronidazole gel, 0.75%, one applicator

(5 g) intravaginally once daily for 5 days Clindamycin, 2% cream, one full applicator vaginally each night for 7 days Examination for sexually transmitted infection; treatment with metronidazole, 2 g PO (single dose) None

features when mixed with saline (motile trichomonads and/or “clue cells”) and with 10% KOH (pseudohyphae or hyphae indicative of vul vovaginal candidiasis). Additional objective laboratory tests, described below, are useful for establishing the cause of abnormal vaginal dis charge. Gram’s staining of vaginal fluid can be used to characterize the vaginal bacteria using the Nugent score but is used primarily for research purposes and requires familiarity with the morphotypes and scale involved. Of note, NAATs that characterize relative concentra tions of BV-associated bacteria and certain Lactobacillus species are now available and offer comparable performance to clinical diagnostic criteria.

TREATMENT Vaginal Discharge Patterns of treatment for abnormal vaginal discharge vary widely. In developing countries, where clinics or pharmacies often dispense treatment based on symptoms alone without examination or test ing, oral treatment with metronidazole—particularly with a 7-day regimen—provides reasonable coverage against both trichomonia sis and BV, the usual causes of symptoms of vaginal discharge. Met ronidazole treatment of sex partners prevents reinfection of women with T. vaginalis, although it does not help prevent the recurrence of BV. Guidelines for syndromic management promulgated by the World Health Organization suggest consideration of treatment for cervical infection and for trichomoniasis, BV, and vulvovaginal can didiasis in women with symptoms of abnormal vaginal discharge. However, it is important to note that the majority of chlamydial and gonococcal cervical infections produce no symptoms. PART 5 Infectious Diseases In industrialized countries, clinicians treating symptoms and signs of abnormal vaginal discharge should, at a minimum, differ entiate between BV and trichomoniasis because optimal manage ment of patients and partners differs for these two conditions. Vaginal Trichomoniasis (See also Chap. 236) Symptomatic trichomoniasis characteristically produces a profuse, yellow, purulent, homogeneous vaginal discharge and vulvar irritation, sometimes with visible inflammation of the vaginal and vulvar epithelium and petechial lesions on the cervix (the so-called strawberry cervix, best visualized by colposcopy). The pH of vaginal fluid—normally <4.7—usually rises to ≥5. Microscopic examination of vaginal discharge mixed with saline reveals motile trichomonads in most culture-positive cases. However, saline microscopy detects fewer than one-half of all cases, and, espe cially in the absence of symptoms or signs, culture or NAAT is usually required for detection of the organism. NAAT for T. vaginalis is more sensitive than culture. Treatment of asymptomatic as well as symptom atic cases reduces rates of transmission and prevents later development of symptoms. TREATMENT Vaginal Trichomoniasis Only nitroimidazoles (e.g., metronidazole and tinidazole) consis tently cure trichomoniasis. A single 2-g oral dose of metronidazole has been the standard treatment for decades, but it is less effective than a weeklong course; the latter is preferred. Tinidazole has a longer half-life than metronidazole, causes fewer gastrointestinal symptoms, and may be useful in treating trichomoniasis that fails to respond to metronidazole. Treatment of sexual partners, facilitated by dispensing metronidazole to the female patient to give to her partner(s), significantly reduces both the risk of reinfection and the reservoir of infection; treating partners is the standard of care. Intravaginal treatment with 0.75% metronidazole gel is not reliable for vaginal trichomoniasis. Thus, systemic use of metronidazole is still recommended throughout pregnancy for treatment of tricho moniasis. In a large randomized trial, metronidazole treatment of trichomoniasis during pregnancy was associated with an increased

frequency of perinatal morbidity. However, most studies, including randomized controlled trials, have shown no adverse effects of met ronidazole use during pregnancy on preterm birth or birth defects. Bacterial Vaginosis BV is a syndrome characterized by symptoms of vaginal malodor and increased white-gray discharge, which appears homogeneous, is low in viscosity, and uniformly covers the vaginal mucosa. BV has been associated with an increased risk of acquiring several other genital infections, including those caused by HIV, C. trachomatis, and N. gonorrhoeae. Other possible risk factors include recent unprotected vaginal intercourse, having a female sex partner, and vaginal douching. Although bacteria associated with BV have been detected under the foreskin of uncircumcised men and have been associated with urethritis, metronidazole treatment of male partners has not reduced the rate of recurrence of BV among affected women. Among women with BV, culture of vaginal fluid has shown mark edly increased prevalences and concentrations of

Gardnerella vaginalis, Mycoplasma hominis, and several anaerobic bacteria (e.g., Mobiluncus, Prevotella [formerly Bacteroides], and some Peptostreptococcus species) as well as an absence of hydrogen peroxide–producing Lactobacillus species that constitute most of the normal vaginal microbiota and help protect against cervical and vaginal infections. Broad-range polymerase chain reaction (PCR) amplification of 16S rDNA in vaginal fluid, with subsequent identification of specific bacterial species by various meth ods, has documented even greater bacterial diversity, including several unique species not previously identified in culture (Fig. 141-2) and Atopobium vaginae, an organism that is strongly associated with BV and is resistant to metronidazole. Other genera newly implicated in BV include Megasphaera, Leptotrichia, Eggerthella, and Dialister. BV is conventionally diagnosed clinically with the Amsel criteria, which include any three of the following four clinical abnormalities: (1) objective signs of increased white homogeneous vaginal discharge; (2) a vaginal discharge pH of >4.5; (3) liberation of a distinct fishy odor (attributable to volatile amines such as trimethylamine) immediately after vaginal secretions are mixed with a 10% solution of KOH; and (4) microscopic demonstration of “clue cells” (vaginal epithelial cells coated with coccobacillary organisms, which have a granular appear ance and indistinct borders; Fig. 141-3) on a wet mount prepared by mixing vaginal secretions with normal saline in a ratio of ~1:1. More recently, NAAT targeting the absence of Lactobacillus crispatus and presence of BV-associated anaerobes have offered accurate options for diagnosing BV. BV6: BVAB-1 (green) + BVAB-2 (red) + DAPI (blue) FIGURE 141-2 Broad-range polymerase chain reaction amplification of 16S rDNA in vaginal fluid from a woman with bacterial vaginosis (BV) shows a field of bacteria hybridizing with probes for BV-associated bacterium 1 (BVAB-1, visible as a thin, curved green rod) and for BVAB-2 (red). The inset shows that BVAB-1 has a morphology similar to that of Mobiluncus (curved rod). (Adapted from DN Fredricks et al: Molecular identification of bacteria associated with bacterial vaginosis. N Engl J Med 353:1899, 2005.)

FIGURE 141-3 Wet mount of vaginal fluid showing typical clue cells from a woman with bacterial vaginosis. Note the obscured epithelial cell margins and the granular appearance attributable to many adherent bacteria (×400). (Photograph provided by Lorna K. Rabe, reprinted with permission from S Hillier et al, in KK Holmes et al [eds]: Sexually Transmitted Diseases, 4th ed. New York, McGraw-Hill, 2008.) TREATMENT Bacterial Vaginosis The standard dosage of oral metronidazole for the treatment of BV is 500 mg twice daily for 7 days. Intravaginal treatment with 2% clindamycin cream (one full applicator [5 g containing 100 mg of clindamycin phosphate] each night for 7 nights) or with 0.75% metronidazole gel (one full applicator [5 g containing 37.5 mg of metronidazole] twice daily for 5 days) is also approved for use in the United States and does not elicit systemic adverse reactions; the response to both of these treatments is similar to the response to oral metronidazole. Another nitroimidazole given orally, secnidazole, is also effective (single 2-g dose). Other alternatives include oral clindamycin (300 mg twice daily for 7 days), clindamycin ovules (100 g
intravaginally once at bedtime for 3 days), and oral tinidazole (1 g daily for 5 days or 2 g daily for 3 days). Unfortunately, recurrence over the long term (i.e., several months later) is distressingly common after either oral or intravaginal treatment. A randomized trial comparing intravaginal gel containing 37.5 mg of metronidazole with a suppository containing 500 mg of metronidazole plus nystatin (the latter not marketed in the United States) showed significantly higher rates of recurrence with the 37.5-mg regimen; this result suggests that higher metronidazole dosages may be important in topical intravaginal therapy. Recurrences can be significantly lessened with the twiceweekly use of suppressive intravaginal metronidazole gel. The goal of replenishing the vaginal

lactobacilli that sustain vaginal health has recently been bolstered by a randomized trial that demonstrated that weekly vaginal administration of L. crispatus CTV-05 (LACTIN-V) reduced rates of recurrent BV by approximately one-third. A meta-analysis of 18 studies concluded that BV during pregnancy substantially increased the risk of preterm delivery and of spontaneous abortion. However, in most studies, topical intravaginal treatment of BV with clindamycin during pregnancy has not reduced adverse pregnancy outcomes. Numerous trials of oral metronidazole treatment during pregnancy have given inconsistent results, and recent reviews have concluded that antenatal treatment of women with BV—including those with previous preterm delivery— did not reduce the risk of preterm delivery. The U.S. Preventive Services Task Force thus recommends against routine screening of pregnant women for BV. Vulvovaginal Pruritus, Burning, or Irritation Vulvovaginal candidiasis produces vulvar pruritus, burning, or irritation, generally without symptoms of increased vaginal discharge or malodor. Genital

herpes can produce similar symptoms, with lesions sometimes difficult to distinguish from the fissures and inflammation caused by candidiasis. Signs of vulvovaginal candidiasis include vulvar erythema, edema, fissures, and tenderness. With candidiasis, a white scanty vaginal discharge sometimes takes the form of white thrush-like plaques or cottage cheese–like curds adhering loosely to the vaginal epithelium. C. albicans accounts for nearly all cases of symptomatic vulvovaginal candidiasis, which probably arise from endogenous strains of C. albicans that have colonized the vagina or the intestinal tract. Complicated vulvovaginal candidiasis includes cases that recur four or more times per year; are unusually severe; are caused by non-albicans Candida species; or occur in women with uncontrolled diabetes, debilitation, immunosuppression, or pregnancy.

In addition to compatible clinical symptoms, the diagnosis of vulvovaginal candidiasis involves the demonstration of pseudohyphae or hyphae by microscopic examination of vaginal fluid mixed with saline or 10% KOH or subjected to Gram’s staining. Microscopic examination is less sensitive than culture but correlates better with symptoms. Culture is typically reserved for cases that do not respond to standard first-line antimycotic agents and is undertaken to rule out imidazole or azole resistance (often associated with Candida glabrata) or before the initiation of suppressive antifungal therapy for recurrent disease. TREATMENT Vulvovaginal Pruritus, Burning, or Irritation Symptoms and signs of vulvovaginal candidiasis warrant treatment, usually intravaginal administration of any of several imidazole antibiotics (e.g., miconazole or clotrimazole) for 3–7 days or of a single dose of oral fluconazole (Table 141-5). Over-the-counter marketing of such preparations has reduced the cost of care and made treatment more convenient for many women with recurrent yeast vulvovaginitis. However, most women who purchase these preparations do not have vulvovaginal candidiasis, whereas many have other vaginal infections that require different treatment. Therefore, only women with classic symptoms of vulvar pruritus and a history of previous episodes of yeast vulvovaginitis documented by an experienced clinician should self-treat. Short-course topical intravaginal azole drugs are effective for the treatment of uncomplicated vulvovaginal candidiasis (e.g., clotrimazole, two 100-mg vaginal tablets daily for 3 days; or miconazole, a 1200-mg vaginal suppository as a single dose). Single-dose oral treatment with fluconazole (150 mg) is also effective and is preferred by many patients. Management of complicated cases (see above) and those that do not respond to the usual intravaginal or single-dose oral therapy often involves prolonged or periodic oral therapy; this situation is discussed extensively in the 2015 CDC STD treatment guidelines (https://www.cdc.gov/ sti/hcp/clinical-

guidance/?CDC_AAref_Val=https://www.cdc.gov/std/ treatment/). Treatment of sexual partners is not routinely indicated. CHAPTER 141 Sexually Transmitted Infections: Overview and Clinical Approach
Other Causes of Vaginal Discharge or Vaginitis In the ulcerative vaginitis associated with staphylococcal toxic shock syndrome, Staphylococcus aureus should be promptly identified in vaginal fluid by Gram's stain and by culture. In desquamative inflammatory vaginitis, smears of vaginal fluid reveal neutrophils, massive vaginal epithelial cell exfoliation with increased numbers of parabasal cells, and grampositive cocci; this syndrome may respond to treatment with 2% clindamycin cream, often given in combination with topical steroid preparations for several weeks. Additional causes of vaginitis and vulvovaginal symptoms include retained foreign bodies (e.g., tampons), cervical caps, vaginal spermicides, vaginal antiseptic preparations or douches, vaginal epithelial atrophy (in postmenopausal women or during prolonged breast-feeding in the postpartum period), allergic reactions to latex condoms, vaginal aphthae associated with HIV infection or Behçet's syndrome, and vestibulitis. ■ ■MUCOPURULENT CERVICITIS Mucopurulent cervicitis (MPC) refers to inflammation of the columnar epithelium and subepithelium of the endocervix and of any contiguous

columnar epithelium that lies exposed in an ectopic position on the ectocervix. MPC in women represents the "silent partner" of urethritis in men, being equally common and often caused by the same agents (N. gonorrhoeae, C. trachomatis, M. genitalium); however, MPC is more difficult than urethritis to recognize, given the nonspecific nature of symptoms (e.g., abnormal vaginal discharge) and the need for visual ization by pelvic examination. As the most common manifestation of these serious bacterial infections in women, MPC can be a harbinger or sign of upper genital tract infection, also known as pelvic inflam matory disease (PID; see below). In pregnant women, MPC can lead to obstetric complications. In the pre-NAAT era, more than one-third of cervicovaginal specimens tested for C. trachomatis, N. gonorrhoeae, M. genitalium, HSV, and T. vaginalis revealed no identifiable etiology for MPC (Fig. 141-4). More recent studies employing NAATs for these pathogens have still failed to identify a microbiologic etiology in nearly one-half of women with MPC. Individual bacteria associated with BV may also elicit an inflammatory reaction at the cervix; thus, BV may be a cause of MPC.

The diagnosis of MPC rests on the detection of cardinal signs at the cervix, including yellow mucopurulent discharge from the cervical os, endocervical bleeding upon gentle swabbing, and edematous cervical ectopy (see below); the latter two findings are somewhat more common with MPC due to chlamydial infection, but signs alone do not allow a distinction among the causative pathogens. Unlike the endocervicitis produced by gonococcal or chlamydial infection, cervicitis caused by HSV produces ulcerative lesions on the stratified squamous epithelium of the ectocervix as well as on the columnar epithelium. Yellow cervi cal mucus on a white swab removed from the endocervix indicates the presence of polymorphonuclear leukocytes (PMNs). Gram's staining may confirm their presence, although it adds relatively little to the diagnostic value of assessment for cervical signs. The presence of ≥20 PMNs per 1000× microscopic field within strands of cervical mucus not contaminated by vaginal squamous epithelial cells or vaginal bac teria indicates endocervicitis. Detection of intracellular gram-negative diplococci in carefully collected endocervical mucus is quite specific but ≤50% sensitive for gonorrhea. Therefore, NAATs for N. gonor rhoeae and C. trachomatis are always indicated in the evaluation of MPC, as is a careful evaluation of vaginal discharge for the causes of vaginitis discussed above. PART 5 Infectious

Diseases MG/GC 2% MG/GC/CT 1% MG/CT 2% HSV 5% GC/CT 7% No organism 35% MG 8% TV 10% CT 17% GC 13% FIGURE 141-4 Organisms detected among female sexually transmitted disease clinic patients with mucopurulent cervicitis (n = 167). CT, Chlamydia trachomatis; GC, gonococcus; HSV, herpes simplex virus; MG, Mycoplasma genitalium; TV, Trichomonas vaginalis. (Courtesy of Dr. Lisa Manhart.)

TREATMENT Mucopurulent Cervicitis Although the above criteria for MPC are neither highly specific nor highly predictive of gonococcal or chlamydial infection in some settings, the 2015 CDC STD guidelines call for consideration of empirical treatment for MPC, pending test results, in most cases. Presumptive treatment with antibiotics active against C. trachomatis should be provided for women at increased risk for this common STI (risk factors: age <25 years, new or multiple sex partners, and unprotected sex), especially if follow-up cannot be ensured. Concurrent therapy for gonorrhea is indicated if the prevalence of this infection is substantial in the relevant patient population (e.g., young adults, a clinic with documented high prevalence). In this situation, therapy should include a single-dose regimen effective for gonorrhea plus treatment for chlamydial infection, as outlined in Table 141-4 for the treatment of urethritis. In settings where gonor rhea is much less common than chlamydial infection, initial therapy for chlamydial infection alone suffices, pending test results for gon orrhea. The etiology and potential benefit of treatment for endocer vicitis not associated with gonorrhea or chlamydial infection have not been established. Although the antimicrobial susceptibility of M. genitalium is not yet well defined, the organism frequently per sists after doxycycline therapy, and it currently seems reasonable to use azithromycin to treat possible M. genitalium infection in such cases. With resistance of M. genitalium to azithromycin now rec ognized, moxifloxacin may be a reasonable alternative. The sexual partner(s) of a woman with MPC should be examined and given a regimen similar to that chosen for the woman unless results of tests for gonorrhea or chlamydial infection in either partner warrant dif ferent therapy or no therapy. ■ ■CERVICAL ECTOPY Cervical ectopy, often mislabeled “cervical erosion,” is easily confused with infectious endocervicitis. Ectopy represents the presence of the one-cell-thick columnar epithelium extending from the endocervix out onto the visible ectocervix. In ectopy, the cervical os may contain clear or slightly cloudy mucus but usually not yellow mucopus. Col poscopy shows intact epithelium. Normally found during adolescence and early adulthood, ectopy gradually recedes through the second and third decades of life, as squamous metaplasia replaces the ectopic columnar epithelium. Oral contraceptive use favors the persistence or reappearance of ectopy, while smoking apparently accelerates squa mous metaplasia. Cauterization of ectopy is not warranted. Ectopy may render the cervix more susceptible to infection with N. gonorrhoeae, C. trachomatis, or HIV. ■ ■PELVIC INFLAMMATORY DISEASE The term pelvic inflammatory disease (PID) usually refers to infection that ascends from the cervix or vagina to involve the endometrium and/or fallopian tubes. Infection can extend beyond the reproductive tract to cause pelvic peritonitis, generalized peritonitis, perihepatitis, perisplenitis, or pelvic abscess. Rarely, infection not related to spe cific sexually transmitted pathogens extends secondarily to the pelvic organs (1) from adjacent foci of inflammation (e.g., appendicitis, regional ileitis, or diverticulitis) or BV, (2) as a result of hematogenous dissemination (e.g., of tuberculosis or staphylococcal bacteremia), or (3) as a complication of certain tropical diseases (e.g., schistosomiasis). Intrauterine infection can be primary (spontaneously occurring and usually sexually transmitted) or secondary to invasive intrauterine sur gical procedures (e.g., dilation and curettage, termination of pregnancy, insertion of an intrauterine device [IUD], or hysterosalpingography) or to parturition. Etiology The agents most often implicated in acute PID include the primary causes of endocervicitis (N. gonorrhoeae, C.

trachomatis, and M. genitalium) and anaerobes associated with BV. In general, PID is most often caused by N. gonorrhoeae in settings where there is a

high incidence of gonorrhea. M. genitalium has also been significantly associated with histopathologic diagnoses of endometritis and with salpingitis. Anaerobic and facultative organisms (especially Prevotella species, peptostreptococci, E. coli, Haemophilus influenzae, and group B strep tococci) as well as genital mycoplasmas have been isolated from the peritoneal fluid or fallopian tubes in a varying proportion (typically one-fourth to one-third) of women with PID studied in the United States. The difficulty of determining the exact microbial etiology of an individual case of PID—short of using invasive procedures for specimen collection—has implications for the approach to empirical antimicrobial treatment of this infection. Epidemiology In the United States, the estimated annual number of initial visits to physicians' offices for PID by women 15–44 years of age fell from an average of 400,000 during the 1980s to 250,000 in 1999 and then to 51,000 in 2014. Hospitalizations for acute PID in the United States also declined steadily throughout the 1980s and early 1990s but have remained fairly constant at 70,000–100,000 per year since 1995. Important risk factors for acute PID include the presence of endocervical infection or BV, a history of salpingitis or of recent vaginal douching, and recent insertion of an IUD. Certain other iatrogenic fac tors, such as dilation and curettage or cesarean section, can increase the risk of PID, especially among women with endocervical gonococcal or chlamydial infection or BV. Symptoms of N. gonorrhoeae–associated and C. trachomatis–associated PID often begin during or soon after the menstrual period; this timing suggests that menstruation is a risk fac tor for ascending infection from the cervix and vagina. Experimental inoculation of the fallopian tubes of nonhuman primates has shown that repeated exposure to C. trachomatis leads to the greatest degree of tissue inflammation and damage; thus, immunopathology probably contributes to the pathogenesis of chlamydial salpingitis. Women using oral contraceptives appear to be at decreased risk of symptomatic PID, and tubal sterilization reduces the risk of salpingitis by preventing intraluminal spread of infection into the tubes. Clinical Manifestations • ENDOMETRITIS: A CLINICAL PATHO LOGIC SYNDROME A study of women with clinically suspected PID who were undergoing both endometrial biopsy and laparoscopy showed that those with endometritis alone differed from those who also had salpingitis in significantly less often having lower quadrant, adnexal, or cervical motion or abdominal rebound tenderness; fever; or elevated C-reactive protein levels. In addition, women with endometri tis alone differed from those with neither endometritis nor salpingitis in more often having gonorrhea, chlamydial infection, and risk factors such as douching or IUD use. Thus, women with endometritis alone were intermediate between those with neither endometritis nor sal pingitis and those with salpingitis with respect to risk factors, clinical manifestations, cervical infection prevalence, and elevated C-reactive protein level. Women with endometritis alone are at lower risk of subsequent tubal occlusion and resulting infertility than are those with salpingitis. SALPINGITIS Symptoms of nontuberculous salpingitis classically evolve from a yellow or malodorous vaginal discharge caused by MPC and/or BV to midline abdominal pain and abnormal vaginal bleeding caused by endometritis and then to bilateral lower abdominal and pelvic pain caused by salpingitis, with nausea, vomiting, and increased abdominal tenderness if peritonitis develops. The abdominal pain in nontuberculous salpingitis is usually described as dull or aching. In some cases, pain is lacking or atypi cal, but active inflammatory changes are found in the course of an unrelated evaluation or procedure, such as a laparoscopic evaluation for infertility. Abnormal uterine bleeding precedes or coincides with the onset of pain in ~40% of women with PID, symptoms of urethritis (dysuria) occur in 20%, and symptoms of proctitis (anorectal pain,

tenesmus, and rectal discharge or bleeding) are occasionally seen in women with gonococcal or chlamydial infection. Speculum examination shows evidence of MPC (yellow endocervi cal discharge, easily induced endocervical bleeding) in the majority of

women with gonococcal or chlamydial PID. Cervical motion tender ness is produced by stretching of the adnexal attachments on the side toward which the cervix is pushed. Bimanual examination reveals uter ine fundal tenderness due to endometritis and abnormal adnexal ten derness due to salpingitis that is usually, but not necessarily, bilateral. Adnexal swelling is palpable in about one-half of women with acute salpingitis, but evaluation of the adnexae in a patient with marked tenderness is not reliable. The initial temperature is >38°C in only about one-third of patients with acute salpingitis. Laboratory findings include elevation of the erythrocyte sedimentation rate (ESR) in 75% of patients with acute salpingitis and elevation of the peripheral white blood cell count in up to 60%.

Unlike nontuberculous salpingitis, genital tuberculosis often occurs in older women, many of whom are postmenopausal. Presenting symp toms include abnormal vaginal bleeding, pain (including dysmenor rhea), and infertility. About one-quarter of these women have had adnexal masses. Endometrial biopsy shows tuberculous granulomas and provides optimal specimens for culture. PERIHEPATITIS AND PERIAPPENDICITIS Pleuritic upper abdominal pain and tenderness, usually localized to the right upper quadrant (RUQ), develop in 3–10% of women with acute PID. Symptoms of perihepatitis arise during or after the onset of symptoms of PID and may overshadow lower abdominal symptoms, thereby leading to a mistaken diagnosis of cholecystitis. In perhaps 5% of cases of acute salpingitis, early laparoscopy reveals perihepatic inflammation ranging from edema and erythema of the liver capsule to exudate with fibrin ous adhesions between the visceral and parietal peritoneum. When treatment is delayed and laparoscopy is performed late, dense “violinstring” adhesions can be seen over the liver; chronic exertional or positional RUQ pain ensues when traction is placed on the adhesions. Although perihepatitis, also known as the Fitz-Hugh–Curtis syndrome, was for many years specifically attributed to gonococcal salpingitis, most cases are now attributed to chlamydial salpingitis. In patients with chlamydial salpingitis, serum titers of microimmunofluorescent anti body to C. trachomatis are typically much higher when perihepatitis is present than when it is absent. CHAPTER 141 Sexually Transmitted Infections: Overview and Clinical Approach
Physical findings include RUQ tenderness and usually include adnexal tenderness and cervicitis, even in patients whose symptoms do not suggest salpingitis. Results of liver function tests and RUQ ultrasonography are nearly always normal. The presence of MPC and pelvic tenderness in a young woman with subacute pleuritic RUQ pain and normal ultrasonography of the gallbladder points to a diagnosis of perihepatitis. Periappendicitis (appendiceal serositis without involvement of the intestinal mucosa) has been found in ~5% of patients undergoing appendectomy for suspected appendicitis and can occur as a complica tion of gonococcal or chlamydial salpingitis. Among women with salpingitis, HIV infection is associated with increased severity of salpingitis and with tuboovarian abscess requiring hospitalization and surgical drainage. Nonetheless, among women with HIV infection and salpingitis, the clinical response to conventional antimicrobial therapy (coupled with drainage of tuboovarian abscess, when found) has usually been satisfactory. Diagnosis Treatment appropriate for PID must not be withheld from patients who have an equivocal diagnosis; it is better to err on the side of overdiagnosis and overtreatment. On the other hand, it is essential to differentiate between salpingitis and other pelvic pathol ogy, particularly surgical

emergencies such as appendicitis and ectopic pregnancy or the chronic syndrome of endometriosis. Nothing short of laparoscopy definitively identifies salpingitis, but routine laparoscopy to confirm suspected salpingitis is gener ally impractical. Most patients with acute PID have lower abdominal pain of <3 weeks' duration, pelvic tenderness on bimanual pelvic examination, and evidence of lower genital tract infection (e.g., MPC). Approximately 60% of such patients have salpingitis at laparoscopy, and perhaps 10–20% have endometritis alone. Among the patients with these findings, a rectal temperature >38°C, a palpable adnexal mass, and elevation of the ESR to >15 mm/h also raise the probability

of salpingitis, which has been found at laparoscopy in 68% of patients with one of these additional findings, 90% of patients with two, and 96% of patients with three. However, only 17% of all patients with lap aroscopy-confirmed salpingitis have had all three additional findings.

In a woman with pelvic pain and tenderness, increased numbers of PMNs (30 per 1000× microscopic field in strands of cervical mucus) or leukocytes outnumbering epithelial cells in vaginal fluid (in the absence of trichomonal vaginitis, which also produces PMNs in vaginal discharge) increase the predictive value of a clinical diagnosis of acute PID, as do onset with menses, history of recent abnormal menstrual bleeding, presence of an IUD, history of salpingitis, and sexual expo sure to a male with urethritis. Appendicitis or another disorder of the gut is favored by the early onset of anorexia, nausea, or vomiting; the onset of pain later than day 14 of the menstrual cycle; or unilateral pain limited to the right or left lower quadrant. Whenever the diag nosis of PID is being considered, serum assays for human β-chorionic gonadotropin should be performed; these tests are usually positive with ectopic pregnancy. Ultrasonography and magnetic resonance imaging (MRI) can be useful for the identification of tuboovarian or pelvic abscess. MRI of the tubes can also show increased tubal diameter, intra tubal fluid, or tubal wall thickening in cases of salpingitis. The primary value of laparoscopy in women with lower abdominal pain is for the exclusion of other surgical problems that cannot be resolved with noninvasive imaging. Some of the most common or seri ous problems that may be confused with salpingitis (e.g., acute appen dicitis, ectopic pregnancy, corpus luteum bleeding, ovarian tumor) are unilateral. Unilateral pain or pelvic mass, although not incompatible with PID, is a strong indication for laparoscopy unless the clinical picture warrants laparotomy instead. Atypical clinical findings such as the absence of lower genital tract infection, a missed menstrual period, a positive pregnancy test, or failure to respond to appropriate therapy are other common indications for laparoscopy. Endometrial biopsy is relatively sensitive and specific for the diagnosis of endometritis, which correlates well with the presence of salpingitis. PART 5 Infectious Diseases Vaginal or endocervical swab specimens should be obtained for NAATs for N. gonorrhoeae and C. trachomatis. At a minimum, vaginal fluid should be evaluated for the presence of PMNs, and endocervical secretions ideally should be assessed by Gram's staining for PMNs and gram-negative diplococci, which indicate gonococcal infection. The clinical diagnosis of PID made by expert gynecologists is confirmed by laparoscopy or endometrial biopsy in ~90% of women who also have cultures positive for N. gonorrhoeae or C. trachomatis. Even among women with no symptoms suggestive of acute PID who were attending an STD clinic or a gynecology clinic in Pittsburgh, endometritis was significantly associated with endocervical gonorrhea or chlamydial infection or with BV, being detected in 26%, 27%, and 15% of women with these conditions, respectively. TREATMENT Pelvic Inflammatory Disease Recommended combination regimens for ambulatory or parenteral management of PID are presented in Table 141-6. Women man aged as outpatients should receive a combined regimen with broad activity,

such as ceftriaxone (to cover possible gonococcal infec tion) followed by doxycycline (to cover possible chlamydial infec tion). Metronidazole should be added to enhance activity against anaerobes; in a randomized trial, the addition of metronidazole to ceftriaxone and doxycycline effected reduction in endometrial anaerobes, M. genitalium, and pelvic tenderness. The CDC STD treatment guidelines recommend initiation of empirical treatment for PID in sexually active young women and other women at risk for PID if they are experiencing pelvic or lower abdominal pain, if no other cause for the pain can be identified, and if pelvic examination reveals one or more of the following criteria for PID: cervical motion tenderness, uterine tenderness, or adnexal tenderness. Women with suspected PID can be treated as either outpatients or inpatients. In the multicenter Pelvic Inflammatory

TABLE 141-6 Combination Antimicrobial Regimens Recommended for Outpatient Treatment or for Parenteral Treatment of Pelvic Inflammatory Disease OUTPATIENT REGIMENSa PARENTERAL REGIMENS Ceftriaxone (500 mg IM once) plus Doxycycline (100 mg PO bid for 14 days) plusb Initiate parenteral therapy with either of the following regimens; continue parenteral therapy until 48 h after clinical improvement; then change to outpatient therapy, as described in the text Regimen A Cefotetan (2 g IV q12h) or cefoxitin (2 g IV q6h) plus Doxycycline (100 mg IV or PO q12h) Regimen B Clindamycin (900 mg IV q8h) plus Gentamicin (loading dose of 2 mg/kg IV or IM, then maintenance dose of 1.5 mg/kg q8h) Metronidazole (500 mg PO bid for 14 days) aSee text for discussion of options in the patient who is intolerant of cephalosporins. bThe addition of metronidazole is recommended particularly if bacterial vaginosis or trichomoniasis is present. Source: Adapted from Centers for Disease Control and Prevention: MMWR Recomm Rep 70(RR-04):1, 2021. Disease Evaluation and Clinical Health (PEACH) trial, 831 women with mild to moderately severe symptoms and signs of PID were randomized to receive either inpatient treatment with IV cefoxitin and doxycycline or outpatient treatment with a single IM dose of cefoxitin plus oral doxycycline. Short-term clinical and microbio logic outcomes and long-term outcomes were equivalent in the two groups. Nonetheless, hospitalization should be considered when (1) the diagnosis is uncertain and surgical emergencies such as appen dicitis and ectopic pregnancy cannot be excluded, (2) the patient is pregnant, (3) pelvic abscess is suspected, (4) severe illness or nausea and vomiting preclude outpatient management, (5) the patient has HIV infection, (6) the patient is assessed as unable to follow or tol erate an outpatient regimen, or (7) the patient has failed to respond to outpatient therapy. Some experts also prefer to hospitalize ado lescents with PID for initial therapy, although younger women do as well as older women on outpatient therapy. Currently, no agents other than parenteral cephalosporins pro vide reliable coverage for gonococcal infection. Thus, adequate oral treatment of women with serious intolerance to cephalosporins is a challenge. If penicillins are an option, amoxicillin/clavulanic acid combined with doxycycline has elicited a short-term clini cal response in one trial. Clinical trials performed outside the United States support the effectiveness of oral moxifloxacin. For women whose PID involves quinolone-resistant N. gonorrhoeae, treatment is uncertain but could include parenteral gentamicin or ertapenem. For hospitalized patients, the following two parenteral regimens (Table 141-6) have given nearly identical results in a multicenter randomized trial:

1. Doxycycline plus either cefotetan or cefoxitin: Administration of these drugs should be continued by the IV route for at least 48 h after the patient’s condition improves and then followed with oral doxycycline (100 mg twice daily) to complete 14 days of therapy.

2. Clindamycin plus gentamicin in patients with normal renal function: Once-daily administration of gentamicin (with com bination of the total daily dose into a single daily dose) has not been evaluated in PID but has been efficacious in other serious infections and could be substituted. Treatment with these drugs should be continued for at least 48 h after the patient's condition improves and then followed with oral doxycycline (100 mg twice daily) or clindamycin (450 mg four times daily) to complete 14 days of therapy. In cases with tuboovarian abscess, clindamycin rather than doxycycline for continued therapy provides better coverage for anaerobic infection.

FOLLOW-UP Hospitalized patients should show substantial clinical improvement within 3–5 days. Women treated as outpatients should be clinically reevaluated within 72 h. A follow-up telephone survey of women seen in an emergency department and given a prescription for 10 days of oral doxycycline for PID found that 28% never filled the prescription and 41% stopped taking the medication early (after an average of 4.1 days), often because of persistent symptoms, lack of symptoms, or side effects. Women not responding favorably to ambulatory therapy should be hospitalized for parenteral therapy and further diagnostic evaluations, including a consideration of laparoscopy. Sex partners should be evaluated and treated empiri cally for gonorrhea and chlamydial infection. After completion of treatment, tests for persistent or recurrent infection with N. gonor rhoeae or C. trachomatis should be performed if symptoms persist or recur or if the patient has not complied with therapy or has been reexposed to an untreated sex partner. SURGERY Surgery is necessary for the treatment of salpingitis only in the face of life-threatening infection (such as rupture or threatened rupture of a tuboovarian abscess) or for drainage of an abscess. Conserva tive surgical procedures are usually sufficient. Pelvic abscesses can often be drained by posterior colpotomy, and peritoneal lavage can be used for generalized peritonitis. Prognosis Late sequelae include infertility due to bilateral tubal occlusion, ectopic pregnancy due to tubal scarring without occlusion, chronic pelvic pain, and recurrent salpingitis. The overall post-salpingitis risk of infertility due to tubal occlusion in a large study in Sweden was 11% after one episode of salpingitis, 23% after two episodes, and 54% after three or more episodes. A University of Washington study found a sevenfold increase in the risk of ectopic pregnancy and an eightfold increase in the rate of hysterectomy after PID. Prevention A randomized controlled trial designed to determine whether selective screening for chlamydial infection reduces the risk of subsequent PID showed that women randomized to undergo screening had a 56% lower rate of PID over the following year than did women receiving the usual care without screening. This report helped prompt U.S. national guidelines for risk-based chlamydial screening of young women to reduce the incidence of PID and the prevalence of post-PID sequelae, while also reducing sexual transmission of C. trachomatis. The CDC and the U.S. Preventive Services Task Force recommend that sexually active women ≤25 years of age be screened annually for genital chlamydial infection. ■

■ULCERATIVE GENITAL OR PERIANAL LESIONS Genital ulceration reflects a set of important STIs, most of which sharply increase the risk of sexual acquisition and shedding of HIV. In a 1996 study of genital ulcers in 10 of the U.S. cities with the highest rates of primary syphilis, PCR testing of ulcer specimens demonstrated HSV in 62% of patients, T. pallidum in 13%, and Haemophilus ducreyi (the cause of chancroid) in 12–20%. Today, genital herpes represents an even higher proportion of genital ulcers in the United States and other industrialized countries, even with a marked increase in early syphilis. In Asia and Africa, chancroid (Fig. 141-5) was once considered the most common type of genital ulcer, followed in frequency by primary syphilis and then genital herpes (Fig. 141-6). With increased efforts to control chancroid and syphilis and widespread use of

broad-spectrum antibiotics to treat STI-related syndromes, together with more frequent recurrences or persistence of genital herpes attributable to HIV infec tion, PCR testing of genital ulcers now clearly implicates genital herpes as by far the most common cause of genital ulceration in most develop ing countries. LGV due to C. trachomatis (Fig. 141-7) and donovanosis (granuloma inguinale, due to Klebsiella granulomatis; see Fig. 178-1) continue to cause genital ulceration in some developing countries. LGV virtually disappeared in industrialized countries during the first 20 years of the HIV pandemic, but outbreaks are again occurring in

FIGURE 141-5 Chancroid: multiple, painful, punched-out ulcers with undermined borders on the labia occurring after autoinoculation. Europe (including the United Kingdom), in North America, and in Australia. In these outbreaks, LGV typically presents as proctitis, with or without anal lesions, in men who report unprotected receptive anal intercourse, very often in association with HIV and/or hepatitis C virus infection; the latter may be an acute infection acquired through the same exposure. Other causes of genital ulcers include (1) candidiasis and traumatized genital warts; (2) lesions due to genital involvement by more widespread dermatoses; (3) cutaneous manifestations of sys temic diseases such as genital mucosal ulceration in Stevens-Johnson syndrome or Behçet's disease; (4) superinfections of lesions that may originally have been sexually acquired (for example, methicillinresistant S. aureus complicating a genital ulcer due to HSV-2); and (5) localized drug reactions, such as the ulcers occasionally seen with topi cal paromomycin cream or boric acid preparations. CHAPTER 141 Sexually Transmitted Infections: Overview and Clinical Approach Diagnosis Although most genital ulcerations cannot be diagnosed confidently on clinical grounds alone, clinical findings (Table 141-7) and epidemiologic considerations can guide initial management (Table 141-8) pending results of specific tests. Clinicians should order a rapid serologic test for syphilis in all cases of genital ulcer and treat presumptively while awaiting serology in a patient at increased FIGURE 141-6 Genital herpes. A relatively mild, superficial ulcer is typically seen in episodic outbreaks. (Courtesy of Michael Remington, University of Washington Virology Research Clinic.)

FIGURE 141-7 Lymphogranuloma venereum (LGV): striking tender lymphadenopathy occurring at the femoral and inguinal lymph nodes, separated by a groove made by Poupart's ligament. This "sign-of-the-groove" is not considered specific for LGV; for example, lymphomas may present with this sign. epidemiologic risk (for example, MSM) or in pregnancy. To evaluate lesions except those highly characteristic of infection with HSV (i.e., those with herpetic vesicles), dark-field microscopy, direct immuno fluorescence, and a NAAT for T. pallidum can be useful but are rarely available. It is important to note that 30% of syphilitic chancres—the primary ulcer of syphilis—are associated with an initially nonreactive syphilis serology. All patients presenting with genital ulceration should be counseled and tested for HIV infection. PART 5 Infectious Diseases Typical vesicles or pustules or a cluster of painful ulcers preceded by vesiculopustular lesions suggest genital herpes. These typical clinical manifestations make detection of the virus optional; however, many patients want confirmation of the diagnosis, and differentiation of HSV-1 from HSV-2 has prognostic implications, because the latter causes more frequent genital recurrences and is more infectious to vulnerable sex partners. Painless, nontender, indurated ulcers with firm, nontender inguinal adenopathy suggest primary syphilis. If results of dark-field examina tion and a rapid serologic test for syphilis are initially negative, or if these tests are not available, presumptive therapy should be provided on the basis of the individual's risk. With historically high rates of syphilis among MSM in the United States, therapy for this infection should not be withheld pending watchful waiting and/or

subsequent TABLE 141-7 Clinical Features of Genital Ulcers FEATURE SYPHILIS HERPES CHANCROID Incubation period 9–90 days 2–7 days 1–14 days 3 days–6 weeks 1–4 weeks (up to 6 months) Early primary lesions Papule Vesicle Pustule Papule, pustule, or vesicle Papule Number of lesions Usually one Multiple Usually multiple, may coalesce Diameter 5–15 mm 1–2 mm Variable 2–10 mm Variable Edges Sharply demarcated, elevated, round, or oval Erythematous Undermined, ragged, irregular Depth Superficial or deep Superficial Excavated Superficial or deep Elevated Base Smooth, nonpurulent, relatively nonvascular Serous, erythematous, nonvascular Induration Firm None Soft Occasionally firm Firm Pain Uncommon Frequently tender Usually very tender Variable Uncommon Lymphadenopathy Firm, nontender, bilateral Firm, tender, often bilateral with initial episode Source: Reproduced with permission from RM Ballard, in KK Holmes et al (eds): Sexually Transmitted Diseases, 4th ed. New York, McGraw-Hill, 2008.

detection of seroconversion. Repeated serologic testing for syphilis 1 or 2 weeks after treatment of seronegative primary syphilis usually demonstrates seroconversion. “Atypical” or clinically trivial ulcers may be more common manifes tations of genital herpes than classic vesiculopustular lesions. Specific tests for HSV in such lesions are therefore indicated (Chap. 197). Com mercially available type-specific serologic tests for serum antibody to HSV-2 may give negative results, especially when patients present early with the initial episode of genital herpes or when HSV-1 is the cause of genital herpes. Furthermore, a positive test for antibody to HSV-2 does not prove that the current lesions are herpetic because nearly one-fifth of the general population of the United States becomes seropositive for HSV-2 during early adulthood. Although even “type-specific” tests for HSV-2 that are commercially available in the United States are not 100% specific, a positive HSV-2 serology does enable the clinician to tell the patient that they have probably had genital herpes, should learn to recognize symptoms, and should avoid sex during recurrences. In addition, because genital shedding and sexual transmission of HSV-2 often occur in the absence of symptoms and signs of recurrent herpetic lesions, persons who have a history of genital herpes or who are sero positive for HSV-2 should consider disclosure of serostatus to partners and the use of condoms or suppressive antiviral therapy, both of which can reduce the risk of HSV-2 transmission to a sexual partner. Demonstration of H. ducreyi by culture (or by PCR, where avail able) is most useful when ulcers are painful and purulent, especially if inguinal lymphadenopathy with fluctuance or overlying erythema is noted; if chancroid is prevalent in the community; or if the patient has recently had a sexual exposure elsewhere in a chancroid-endemic area (e.g., a developing country). Enlarged, fluctuant lymph nodes should be aspirated for culture or PCR to detect H. ducreyi as well as for Gram’s staining and culture to rule out the presence of other pyogenic bacteria. When genital ulcers persist beyond the natural history of initial episodes of herpes (2–3 weeks) or of chancroid or syphilis (up to 6 weeks) and do not resolve with syndrome-based antimicrobial therapy, then— in addition to the usual tests for herpes, syphilis, and chancroid— biopsy is indicated to exclude donovanosis as well as carcinoma and other nonvenereal dermatoses. TREATMENT Ulcerative Genital or Perianal Lesions Immediate syndrome-based treatment for acute genital ulcer (after collection of all necessary diagnostic specimens at the first visit) is often appropriate before all test results become available because patients with typical initial or recurrent episodes of genital or LYMPHOGRANULOMA VENEREUM DONOVANOSIS Usually one; often not detected, despite lymphadenopathy Variable Elevated, round, or oval Elevated, irregular Purulent, bleeds easily Variable, nonvascular Red and velvety, bleeds readily Tender, may suppurate, loculated, usually unilateral Tender, may suppurate, loculated, usually unilateral None; pseudobuboes

TABLE 141-8 Initial Management of Genital or Perianal Ulcer Causative Pathogens HSV Treponema pallidum (primary syphilis) Haemophilus ducreyi (chancroid) Usual Initial Laboratory Evaluation Dark-field examination (if available), direct FA, or PCR for T. pallidum RPR, VDRL, or EIA serologic test for syphilisa Culture, direct FA, ELISA, or PCR for HSV HSV-2-specific serology (consider) In chancroid-endemic area: PCR or culture for H. ducreyi Initial Treatment Herpes confirmed or suspected (history or sign of vesicles): Treat for genital herpes with acyclovir, valacyclovir, or famciclovir. Syphilis confirmed (dark-field, FA, or PCR showing T. pallidum, or RPR reactive): Benzathine penicillin (2.4 million units IM once to patient, to recent [e.g., within

3 months] seronegative partner[s], and to all recent partners)b Chancroid confirmed or suspected (diagnostic test positive, or HSV and syphilis excluded, and persistent lesion): Ciprofloxacin (500 mg PO as single dose) or Ceftriaxone (250 mg IM as single dose) or Azithromycin (1 g PO as single dose) aIf results are negative but primary syphilis is suspected, treat presumptively when indicated by epidemiologic and sexual risk assessment; repeat in 1 week. bThe same treatment regimen is also effective in HIV-infected persons with early syphilis. Abbreviations: EIA, enzyme immunoassay; ELISA, enzyme-linked immunosorbent assay; FA, fluorescent antibody; HSV, herpes simplex virus; PCR, polymerase chain reaction; RPR, rapid plasma reagin; VDRL, Venereal Disease Research Laboratory. anorectal herpes can benefit from prompt oral antiviral therapy (Chap. 197); because early treatment of sexually transmitted causes of genital ulcers decreases further transmission; and because some patients do not return for test results and treatment. A thorough assessment of the patient’s sexual-risk profile and medical history is critical in determining the course of initial management. The patient who has risk factors consistent with exposure to syphilis (e.g., a male patient who reports sex with other men or who has HIV infection) should generally receive initial treatment for syphi lis. Empirical therapy for chancroid should be considered if there has been an exposure in an area of the world where chancroid occurs or if regional lymph node suppuration is evident. Finally, empirical antimicrobial therapy may be indicated if ulcers persist and the diagnosis remains unclear after a week of observation despite attempts to diagnose herpes, syphilis, and chancroid. ■ ■PROCTITIS, PROCTOCOLITIS, ENTEROCOLITIS, AND ENTERITIS Sexually acquired proctitis, with inflammation limited to the rectal mucosa (the distal 10–12 cm), results from direct rectal inoculation of typical STD pathogens. In contrast, inflammation extending from the rectum to the colon (proctocolitis), involving both the small and the large bowel (enterocolitis), or involving the small bowel alone (enteritis) can result from ingestion of typical intestinal pathogens through oral– anal exposure during sexual contact. Anorectal pain and mucopuru lent, bloody rectal discharge suggest proctitis or proctocolitis. Proctitis commonly produces tenesmus (causing frequent attempts to defecate, but not true diarrhea) and constipation, whereas proctocolitis and enterocolitis more often cause true diarrhea. In all three conditions, anoscopy usually shows mucosal exudate and easily induced mucosal bleeding (i.e., a positive “wipe test”), sometimes with petechiae or mucosal ulcers. Exudate should be sampled for Gram’s staining and other microbiologic studies. Sigmoidoscopy or colonoscopy shows inflammation limited to the rectum in proctitis or disease extending at least up into the sigmoid colon in proctocolitis. Acquisition of HSV, N. gonorrhoeae, or C. trachomatis (including LGV strains of C. trachomatis) during receptive anorectal intercourse

causes most cases of infectious proctitis in women and MSM. Primary and secondary syphilis can also produce anal or anorectal lesions, with or without symptoms. Gonococcal or chlamydial proctitis typically involves the most distal rectal mucosa and the anal crypts and is clini cally mild,

without systemic manifestations. In contrast, primary proc titis due to HSV and proctocolitis due to the strains of C. trachomatis that cause LGV usually produce severe anorectal pain and often cause fever. Perianal ulcers and inguinal lymphadenopathy, most commonly due to HSV, can also occur with LGV or syphilis. Sacral nerve root radiculopathies, usually presenting as urinary retention, laxity of the anal sphincter, or constipation, may complicate primary herpetic proc titis. In LGV, rectal biopsy typically shows crypt abscesses, granulomas, and giant cells—findings resembling those in Crohn's disease; such findings should always prompt rectal culture and serology for LGV, which is a curable infection. Syphilis can also produce rectal granu lomas, usually in association with infiltration by plasma cells or other mononuclear cells. Syphilis, LGV, and HSV infection involving the rectum can produce perirectal adenopathy that is sometimes mistaken for malignancy; syphilis, LGV, HSV infection, and chancroid involving the anus can produce inguinal adenopathy because anal lymphatics drain to inguinal lymph nodes.

Diarrhea and abdominal bloating or cramping pain without ano rectal symptoms and with normal findings on anoscopy and sigmoid oscopy occur with inflammation of the small intestine (enteritis) or with proximal colitis. In MSM without HIV infection, enteritis is often attributable to Giardia lamblia. Sexually acquired proctocolitis is most often due to Campylobacter or Shigella species. CHAPTER 141 TREATMENT Proctitis, Proctocolitis, Enterocolitis, and Enteritis Acute proctitis in persons who have practiced receptive anorec tal intercourse is usually sexually acquired. Such patients should undergo anoscopy to detect rectal ulcers or vesicles and petechiae after swabbing of the rectal mucosa; to examine rectal exudates for PMNs and gram-negative diplococci; and to obtain rectal swab specimens for testing for rectal gonorrhea, chlamydial infection, herpes, and syphilis. Pending test results, patients with proctitis should receive empirical syndromic treatment—e.g., with ceftriax one (a single IM dose of 500 mg for gonorrhea) plus doxycycline (100 mg by mouth twice daily for 7 days for possible chlamydial infection) plus treatment for herpes or syphilis if indicated. If LGV proctitis is proven or suspected, the recommended treatment is doxycycline (100 mg by mouth twice daily for 21 days); alterna tively, 1 g of azithromycin once a week for 3 weeks is likely to be effective but is little studied. Sexually Transmitted Infections: Overview and Clinical Approach
PREVENTION AND CONTROL OF STIs Prevention and control of STIs require the following:

1. Reduction of the average rate of sexual exposure to STIs through alteration of sexual risk behaviors and behavioral norms among both susceptible and infected persons in all population groups. The necessary changes include reduction in the total number of sexual partners and the number of concurrent sexual partners. The U.S. Preventive Services Task Force recommends intensive behavioral counseling for all sexually active adolescents and adults who are at increased risk for STIs (grade B recommendation). Motivational interviewing is one approach that has elicited behavioral changes, including safer sex practices and more consistent contraception, that contribute to these goals.
2. Reduction of the efficiency of transmission through the promo tion of safer sexual practices, the use of condoms during casual or commercial sex, vaccination against HBV and HPV infection, male circumcision (which reduces risk of acquisition of HIV infec tion, chancroid, and perhaps other STIs), and a growing number of other approaches (e.g., early detection and treatment of other STIs to reduce the efficiency of sexual transmission of HIV; provision of

Number whose behaviors and ecologic settings result in exposure to STDs Number who acquire STDs Number who develop symptoms of STDs Number who perceive the symptoms of STDs Number who promptly seek medical care when symptomatic Number seeking care who have ready access to care Number perceived by clinicians as possibly having STDs Number perceived as possibly having STDs who can be tested for STDs Number with objective evidence of STDs who get proper treatment for STDs Number who comply with treatment Number whose partners are treated and who are not reinfected FIGURE 141-8 Critical control points for preventive and clinical interventions against sexually transmitted diseases (STDs). (Adapted from HT Waller and MA Piot: Bull World Health Organ 41:75, 1969 and 43:1, 1970; and from “Resource allocation model for public health planning—a case study of tuberculosis control,” Bull World Health Organ 48[Suppl], 1973.) doxycycline for PEP). Among MSM and transgender women, doxy cycline PEP (200 mg taken once orally within 72 h of condomless sex, with a maximum dose of 200 mg each day) can reduce the risk of chlamydia, syphilis, and, in some studies, gonorrhea. However, studies have failed to demonstrate efficacy among cisgender women. 3. Shortening of the duration of infectivity of STIs through early detec PART 5 Infectious Diseases tion and curative or suppressive treatment of patients and their sexual partners. Financial and time constraints imposed by many clinical practices, along with the reluctance of some clinicians to ask questions about stigmatized sexual behaviors, often curtail screening and prevention services. As outlined in Fig. 141-8, the success of clinicians’ efforts to detect and treat STIs depends in part on societal efforts to teach young people how to recognize symptoms of STIs; to motivate individuals with symptoms to seek care promptly; to educate persons who are at risk but have no symptoms about what tests they should undergo routinely; and to make high-quality, appropriate care accessible, afford able, and acceptable, especially to the young indigent patients most likely to acquire an STI. STI RISK ASSESSMENT Because many infected individuals develop no symptoms or fail to recognize and report symptoms, clinicians should routinely perform an STI risk assessment for teenagers and young adults as a guide to selec tive screening. As stated earlier, the U.S. Preventive Services Task Force recommends screening sexually active female patients ≤25 years of age for C. trachomatis whenever they present for health care (at least once a year); older women should be tested if they have more than one sexual partner, have begun a new sexual relationship since the previous test, or have another STI diagnosed. In women 25–29 years of age, chlamydial infection is uncommon but still may reach a prevalence of 3–5% in some settings; information provided by women in this age group on a sex partner’s concurrency (whether a male partner has had another sex partner during the time they have been together) is helpful in iden tifying women at increased risk. In some regions of the United States, widespread selective screening and treatment of young women for cervical C. trachomatis infection have been associated with a 50–60% drop in prevalence. Such screening and treatment also protect the individual woman from PID. Sensitive urine-based genetic amplifica tion tests permit expansion of screening to men, teenage boys, and girls in settings where examination is not planned or is impractical (e.g.,

during preparticipation sports examinations or during initial medical evaluation of adolescent girls). Vaginal swabs—collected either by the health care provider at a pelvic examination or by the woman herself— are highly sensitive and specific for the diagnosis of chlamydial and gonococcal infection; they are now the preferred type of specimen for screening and diagnosis of these infections. Although gonorrhea is now substantially less common than chla mydial infection in women in industrialized countries, screening tests for N. gonorrhoeae are still appropriate for women and teenage girls attending STD clinics and for sexually active teens and young women from areas of high gonorrhea prevalence. Multiplex NAATs that com bine screening for N.

gonorrhoeae and C. trachomatis—and, more recently, for T. vaginalis—in a single low-cost assay now facilitate the prevention and control of these infections for populations at high risk. All patients who have newly detected STIs or are at high risk for STIs according to routine risk assessment as well as all pregnant women should be encouraged to undergo serologic testing for syphilis and HIV infection, with appropriate counseling. Randomized trials have shown that risk-reduction counseling of patients with STIs significantly lowers subsequent risk of acquiring an STI; such counseling should now be considered a standard component of STI management. Preimmuniza tion serologic testing for antibody to HBV is indicated for unvaccinated persons who are known to be at high risk, such as MSM and people who use injection drugs. In most young persons, however, it is more cost-effective to vaccinate against HBV without serologic screening. It is important to recognize that, while immunization against HBV has contributed to marked reductions in the incidence of infection with this virus, the majority of new cases that occur are acquired through sex. In 2006, the CDC's Advisory Committee on Immunization Prac tices (ACIP) recommended the following: (1) Universal hepatitis B vaccination should be implemented for all unvaccinated adults in set tings in which a high proportion of adults have risk factors for HBV infection (e.g., STD clinics, HIV testing and treatment facilities, drugabuse treatment and prevention settings, health care settings targeting services to injection drug users or MSM, and correctional facilities). (2) In other primary care and specialty medical settings that provide care to adults at risk for HBV infection, health care providers should inform all patients about the health benefits of vaccination, the risk factors for HBV infection, and the persons for whom vaccination is recommended; they should vaccinate adults who report risk factors for HBV infection as well as any adult who requests protection from HBV infection. To promote vaccination in all settings, health care providers should implement standing orders to identify adults recommended for hepatitis B vaccination, should administer hepatitis B vaccine as part of routine clinical services, should not require acknowledgment of an HBV infection risk factor for adult vaccination, and should use available reimbursement mechanisms to remove financial barriers to hepatitis B vaccination. In 2007, the ACIP made its first recommendation for routine immu nization of 9- to 26-year-old girls and women with the quadrivalent HPV vaccine (against HPV types 6, 11, 16, and 18). In 2011, the ACIP recommended routine administration of quadrivalent HPV vaccine to boys at 11 or 12 years of age and to males 13–21 years of age who have not yet been vaccinated or who have not completed the three-dose vac cine series; HBV vaccination of men 22–26 years of age has also been recommended. Since that time, a nonavalent HPV vaccine has become available and has largely replaced the earlier vaccines. Moreover, single-dose HPV vaccine has great promise to simplify implementation without compromising efficacy. The optimal age for recommended vaccination is 11–12 years because of the very high risk of HPV infec tion after sexual debut. Partner management is the process of identifying and informing partners of infected patients about possible exposure to an STI and of examining, testing, vaccinating, and treating partners as appropriate. In a series of 22 reports concerning partner notification during the 1990s, index patients with gonorrhea or chlamydial infection named a mean of 0.75–1.6 partners, of whom one-fourth to one-third were infected; those with syphilis named 1.8–6.3 partners, with one-third to one-half infected; and those with HIV infection named 0.76–5.31 partners, with

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