TABLE 105.2 Treatment of Implant-Associated Infections—cont'd

MICROORGANISM	ANTIMICROBIAL AGENT[a]	DOSE	ROUTE
Mixed infections (without methicillin-resistant staphylococci)	Ampicillin-sulbactam *or* Amoxicillin-clavulate[q] *or* Piperacillin-tazobactam *or* Imipenem *or* Meropenem for 2–4 wk, *followed by* individual regimens according to antimicrobial susceptibility	3 g q6h 2.2 g q6h 4.5 g q6h–q8h 500 mg q6h–q8h 1 g q8h[p]	IV IV IV IV IV

Antimicrobial dosage recommendations are based on normal renal and hepatic function. Antimicrobials should be chosen based on in vitro susceptibility, patient drug allergies and intolerances, and potential drug interactions or contraindications to a specific antimicrobial.
[a]For total duration of antimicrobial treatment, see text.
[b]Other dosages and intervals of administration have been reported with equivalent success rates.[145]
[c]In patients with delayed hypersensitivity, cefazolin (2 g q8h IV) can be administered. In patients with immediate hypersensitivity, penicillin should be replaced by vancomycin.
[d]Recommended doses are based on AUC_{0-24}/MIC and trough levels. Trough levels should be monitored for nephrotoxicity.[216]
[e]Recommended dose according to Infectious Diseases Society of America (IDSA) guidelines.[7] However, doses up to 10 mg/kg q24h are reported.[155]
[f]Teicoplanin: Loading dose (days 1–3 of treatment) 800 mg q24h is recommended. Not available in the United States.
[g]Double strength = trimethoprim 160 mg plus sulfamethoxazole 800 mg.
[h]Lack of data on bone penetration. Alternatively, doxycycline 100 mg q12h PO is possible.[35]
[i]Higher doses PO (e.g., up to 2400 mg/day) are possible but frequently not tolerated owing to side effects.
[j]We recommend determination of minimal inhibitory concentration for penicillin.
[k]Combination therapy with an aminoglycoside is optional because its superiority to monotherapy in PJI is unproven.[217] When using combination therapy, monitor for signs of ototoxicity and nephrotoxicity of aminoglycosides; the latter is potentiated with other nephrotoxic agents (e.g., vancomycin).
[l]In patients with hypersensitivity to penicillin, see treatment options for penicillin-resistant enterococci.
[m]In patients with hypersensitivity to β-lactam, ciprofloxacin can be administered.
[n]Cetriaxone and ceftazidime should not be administered for *Enterobacter* spp., even when tested susceptible in the laboratory. We recommend determination of MIC for cefepime. In infections due to *Enterobacter* spp., ertapenem 1 g q24h can be administered alternatively. Ertapenem is not effective against *Pseudomonas* spp. and other nonfermenters.
[o]Dosage recommended according to IDSA guidelines.[7] In Europe, 2 g q8h is suggested in case of *P. aeruginosa* infection.[35]
[p]Addition of aminoglycoside is optional.[7]
[q]Not available in the United States as IV drug.
AUC_{0-24}, Area under the time-concentration curve from time 0 to 24 hours; *DS,* double-strength; *MIC,* minimal inhibitory concentration.
Modified from Zimmerli W, Trampuz A, Ochsner PE. Prosthetic-joint infections. N Engl J Med. *2004;351:1645–1654; Sendi P, Zimmerli W. Antimicrobial treatment concepts for orthopaedic device-related infection.* Clin Microbiol Infect. *2012;18:1176–1184; and Osmon D, Berbari E, Berendt A, et al. Diagnosis and management of prosthetic joint infection: clinical practice guidelines by the Infectious Diseases Society of America.* Clin Infect Dis. *2013;56:e1–e25.*

similar outcome results with 3-month regimens, in particular when patient selection and treatment were according to protocol.[38,125,135] The treatment course can be shortened to 6 weeks in patients treated with two-stage exchange with a long interval (see Fig. 105.2).

Initial intravenous therapy for 1 to 2 weeks is followed by long-term oral antibiotics. Oral compounds that are used in bone and joint infection should have good bioavailability and reasonable bone penetration.[35,36,38,140–144] Optimal therapy is best defined in staphylococcal implant infections. Rifampin has excellent activity on susceptible biofilm staphylococci. This has been proven in vitro, in animal models, and in several clinical studies.[25,34,36,144] There are no clinical studies proving superiority of rifampin combinations in other gram-positive or gram-negative PJIs.[35] Rifampin must always be combined with another drug for prevention of emergence of resistance. Owing to the risk of superinfection with rifampin-resistant staphylococci from the skin microbiome, we propose starting rifampin combination only in patients with dry wounds—that is, several days after definitive surgery.[145] In addition, we do not use rifampin in the short-interval concept in patients undergoing two-stage exchange. Fluoroquinolones are the first choice for the combination.[3,7,36] Because of increasing resistance, other combinations may be necessary. For each combination, possible interactions with rifampin should be considered.[146] Rifampin should be reserved for patients with implant retention, with one-stage exchange, or after early reimplantation in two-stage exchange. It has no advantage in patients with suppressive therapy and should therefore be discouraged with this type of treatment. Diligent use of rifampin lowers the risk for emergence of resistance.[147]

Because the susceptibility of methicillin-resistant staphylococci to vancomycin is decreasing, novel antistaphylococcal drugs, such as linezolid and daptomycin, may be necessary for the treatment of PJI.[148] Notably, neither is approved for bone and joint infections. Linezolid surpasses the minimal inhibitory concentration in 90% of isolates (MIC_{90}) of enterococci and staphylococci and has a good penetration in human bone.[149] Despite several observational studies in humans, linezolid efficacy in PJI cannot be unambiguously judged.[150–152] According to an observational noncomparative study, in patients with implant retention, monotherapy had a lower cure rate than combination therapy with rifampin. Notably, the best cure rate with implant retention was observed in patients with acute infections and combination therapy.[142] Serious adverse events of long-term linezolid must be considered, including peripheral neuropathy, optic neuritis, and bone marrow suppression. Because bone and joint infections generally require prolonged treatment, the use of linezolid remains controversial.

Daptomycin monotherapy has a low cure rate in animal models of implant-associated infections. However, in combination with rifampin it was highly efficacious in animal models of implant-associated infections.[153,154] Moreover, in contrast to vancomycin, daptomycin combination therapy completely prevented the emergence of rifampin resistance in *S. aureus*.[153] However, the efficacy of daptomycin for PJI cannot be conclusively judged because there are not enough clinical data. If daptomycin is considered for selected cases, the available data point toward treatment regimens with doses ranging from 8 mg/kg up to 10 mg/kg once daily and combination with rifampin.[155] During prolonged treatment, creatinine phosphokinase surveillance is necessary to rapidly detect muscle toxicity. Comedication with statins should be avoided. Also, in case of fever and dyspnea, eosinophilic pneumonia, a rare but life-threatening complication in patients with daptomycin therapy, should be considered.[156]

PJI due to gram-negative bacilli is diagnosed in 10% to 15% of the cases. The risk for these microorganisms is higher in previously treated patients.[157] Patients with gram-negative PJI who qualify for débridement and retention have a good outcome, provided that treatment with a fluoroquinolone is possible, after initial intravenous therapy (see Table 105.2).[37,38,157,158] The rationale for favoring fluoroquinolones is their activity against gram-negative biofilms.[28,37,38,159]

INTERNAL FIXATION–ASSOCIATED INFECTION

Metal hardware for internal fixation of bone fractures, spinal fusions, and corrections of scoliosis are included in this category. Although there are several similarities between the management of PJI and internal fixation–associated infections, there are also important differences. First,

eradication of infection is not always a priority, because the device could be removed after fracture healing or because bridging until definitive stabilization is possible with an external fixation device. Removal of hardware spine implants is often less optional. Second, exogenous infection after surgical treatment for open fractures plays a more important role than in PJI. Third, there is a large variety of anatomic locations where orthopedic devices are fixed, and a large variety of hardware is implanted (e.g., plates, screws, nails, rods), illustrating heterogeneous clinical constellations. Fourth, the involvement of a plastic surgeon for soft tissue coverage after infection in trauma cases plays a more important role than in PJI. The proposed treatment concepts are mainly based on observations and expert opinions. Although the interaction between microorganisms and metal work is similar in PJI and internal fixation–associated infections, classification and management concepts differ.

Definition

There are no commonly accepted criteria for the definition of internal fixation–associated infections. A consensus definition for fracture-related infections was proposed, using suggestive and confirmatory criteria.[160] A combination of clinical, laboratory, imaging, microbiologic, and histopathologic criteria is used to diagnose internal fixation–associated infections. The definition for the histopathologic criterion is not established. It should not be extrapolated from PJI (i.e., polymorphonuclear leukocyte count), because sterile bone necrosis may cause locally limited cellular inflammation. Nonetheless, histopathologic examination can be helpful in establishing the diagnosis (e.g., specific staining for mycobacteria or fungi). Significant growth of microorganisms in sonicate or conventional culture of the device, or growth of the same microorganisms in at least two biopsy samples in proximity to the device, defines infection. In addition to other criteria, a single biopsy sample with growth of a virulent pathogen (e.g., *S. aureus*) may be sufficient to fulfill infection definition. Additional signs of infection are bone loss around metal screws or an intramedullary rod (e.g., nonunion), fluid accumulation around the device, or a draining sinus.

Incidence of Infection

After internal fixation of closed fractures, the incidence of infection is <2%.[161] In patients with open fracture, the incidence of infection gradually increases with the extent of soft tissue damage. Open fractures are generally classified according to the system of Gustilo and colleagues[162] (Table 105.3). Based on this classification, it can be stated that the more severe the open fracture, the higher the incidence of infection. The classification was developed for tibial fractures, but in clinical practice the risk of infection is extrapolated to other anatomic locations. In a systematic review of the literature including 32 studies with 3060 open tibial fractures, type I fracture had an infection rate of 1.8%, and type IIIC 16.1% (see Table 105.3).[163] The use of vacuum-assisted closure may increase the risk of infection.[164]

TABLE 105.3 Open Fracture Classification According to Gustilo et al. and Corresponding Postoperative Infection Rates

FRACTURE TYPE	DESCRIPTION	INFECTION RATE
Type I	Wound is <1 cm long with a clean piercing puncture	1.8%
Type II	Laceration is >1 cm long, no extensive soft tissue damage, the puncture wound is moderately contaminated	3.3%
Type IIIA	Extensive laceration with adequate coverage of the fractured bone	5.0%
Type IIIB	Extensive loss of soft tissue with periosteal stripping and exposure of bone resulting in massive contamination	12.3%
Type IIIC	Open fracture with an arterial injury regardless of the degree of soft tissue injury	16.1%

TABLE 105.4 Classification and Characteristics of Internal Fixation Device–Associated Osteomyelitis

TIME OF ONSET OF SYMPTOMS	CHARACTERISTICS
Early infection (≤2 weeks after implantation)	*Clinical picture:* Signs of wound infection such as persistent fever, pain, erythema, swelling, wound healing disturbances *Typical microorganisms: Staphylococcus aureus,* group A streptococci, gram-negative bacilli
Delayed infection (weeks 3–10 after implantation)	*Clinical picture:* Persisting pain, low-grade fever, mechanical instability, sinus tract *Typical microorganisms:* Low-virulence microorganisms such as coagulase-negative staphylococci or mixed skin flora in case of a sinus tract
Late infection (>10 weeks after implantation)	*Clinical picture:* (1) **acute** hematogenous infection—sepsis syndrome, local pain and signs of inflammation, (2) **chronic** (delayed infection or recurrence of incorrectly treated early infection)—signs of infection after interval with bridging symptoms such as pain, wound-healing disturbances, nonunion *Typical microorganisms:* (1) *S. aureus, Escherichia coli,* (2) any microorganism, including polymicrobial infection

Pathogenesis and Classification

Similar to PJI, the two major routes of infection are exogenous and hematogenous. The relative risk for hematogenous infections is considerably lower than in patients with prosthetic joints. The exogenous route is dominant either via wound contamination due to a penetrating trauma (e.g., open fracture) or via inoculation of microorganisms into the surgical wound during or immediately after surgery (perioperative). In spinal fusions, breakdown of the skin over the hardware can also lead to exogenous infection. In addition, infection may occur via an adjacent ongoing infection, such as skin infection and soft tissue infection (contiguous). On the basis of these routes of infections, internal fixation devices can be classified into:

- Hematogenous
- Exogenous (perioperative or penetrating event)
- Contiguous

A classification according to the time interval from index surgery to infection manifestation is helpful for clinical practice, because it considers three typical features of pathogenesis: (1) infection route, (2) microorganisms, and (3) findings of clinical examination (Table 105.4).[2,165] Early and delayed infections are mainly acquired during trauma (e.g., open fracture) or implant surgery (deep surgical site infection). Early infection is generally caused by high-virulence, and delayed infection by low-virulence, microorganisms. Alternatively, delayed manifestation may be due to postponed early infection. This mainly occurs if a suspected superficial surgical site is treated with empirical antimicrobial therapy without appropriate diagnostic workup. Clinical presentation of late infections can be subclassified into acute and chronic. Acute late infection without bridging symptoms after surgery is typically caused by hematogenous seeding. Chronic late infection occurs as a result of a missed delayed infection or recurs after an inadequately treated early infection. Thus the association among infection route, microorganisms, and time point of clinical presentation cannot be reliably applied in chronic late infections. The corresponding time intervals for this classification (early, within 2 weeks; delayed, occurring in weeks 3 through 10; late, after the 10th week following surgery) have not been scientifically validated[165] but have been used in clinical practice for several decades in the context of a detailed patient history.[166] In early infections, the time of infection

can often be reliably estimated. For the decision regarding surgical management, other criteria than this classification are important (e.g., fracture stability, implant loosening, bone healing).

Microbiology

As in PJI, staphylococci are the most commonly isolated microorganisms in patients with internal fixation device–associated infections. In a study reporting microbiologic data from 777 patients with orthopedic device–associated infection or PJI, the following microorganisms were detected[167]:

- *S. aureus,* 43.5%
- Coagulase-negative staphylococci, 32.9%
- *Streptococcus* spp., 9.0%
- Gram-negative aerobic bacilli, 7.6%
- Enterococci, 3.7%
- Anaerobic bacteria, 0.1%
- Fungi, 1.2%

Regional epidemiologic data about methicillin-resistant *S. aureus* (MRSA) vary considerably among different countries.

In case of open fractures with exposed bone, a polymicrobial flora (including bacteria from the environment) contaminates the wound. Preemptive antimicrobial therapy is often administered to reduce the infection rate. A prolonged course may lead to a selection of one or more resistant microorganisms because no compound is active against all pathogens. For this reason antimicrobial agents with broad spectrum should be avoided.

Clinical Manifestations

The clinical presentation depends on the following variables:

- History of surgical procedure and preceding trauma
- Anatomic localization and surrounding soft tissue
- Time interval between inoculation (e.g., trauma, surgery) and infection manifestation
- Type of microorganism

Symptoms are either acute or chronic. Acute infections manifest typically either early after surgery or late. In early infections, poor wound healing and signs of a surgical site infection such as erythema and wound discharge are the main findings. Wound edge necrosis and hematoma are important risk factors for internal fixation–associated infections. Consequently, clinical signs of poor wound healing after internal fixation placement should rapidly raise the suspicion of infection. Acute infections are frequently caused by virulent pathogens (e.g., *S. aureus*, β-hemolytic streptococci). In acute infections that manifest late, there are two entities with slightly different clinical presentations. In the case of microbial seeding from a distant focus—which can occur any time after surgery—a recent or present history of fever and chills after an uneventful postoperative period, and elevated systemic inflammatory parameters are found. The patient has local pain, but objective signs of a local infection are initially missing. They typically appear only several days after bacterial seeding. The obvious appearance of these local findings depends on the thickness of the soft tissue covering the implant (e.g., visibility at femur versus lower tibia). Therefore it is crucial to have a high degree of suspicion in order to rapidly identify these cases. The second type of acute infection after an uneventful postoperative period is posttraumatic osteomyelitis. In this entity, previous latent infection is reactivated. This may occur even many years or decades after the device has been removed and the bone has apparently healed.[168,169] In the perspective of terminology, these infections are difficult to classify because the fracture is healed, infection pathogenesis is chronic, symptoms are acute, and reoccurrence is late. The dominating symptom is pain. Systemic inflammatory signs such as fever and chills are less frequent than in acute hematogenous cases. The keys to diagnosis are therefore the patient's history and imaging studies performed before invasive procedures. It is, however, not completely clear how and why virulent bacteria reactivate from a dormant state, causing acute symptoms, and it is not yet known what triggers this.

Infections with chronic symptoms occur either in a delayed fashion or late after internal fixation (see Table 105.4). They are due to low-virulence microorganisms (e.g., coagulase-negative staphylococci) or occur after inadequate initial treatment of any microorganism. Although initial wound healing can be observed in these infections, patients often have persisting pain or local signs of inflammation, such as intermittent discharge (sinus tract) or fluctuating erythema in the area of the scar. Impaired bone healing can be seen in imaging investigations. Again, depending on the anatomic localization, clinical signs in the surrounding soft tissue may be completely absent. CRP and ESR typically remain elevated at low levels.

Diagnostic Procedures

The benefit and the sensitivity and specificity of means to diagnose internal fixation device–associated infections mainly depend on the time interval between surgery and infection. All infections should be clinically evaluated by a multidisciplinary team of experts. In early infections, CRP, ESR, and blood leukocyte counts are not helpful to predict infection. When serial CRP measurements are performed, infection should be suspected in the case of persistent high values or significant increase after a postoperative decline. Imaging plays a minor role in patients with early infections. However, both laboratory tests and imaging may be helpful in the delayed and late period.

Microbiology and Histopathology

When infection is suspected, surgical exploration and sampling are required. Three to six biopsy specimens should be obtained in order to optimize sensitivity and specificity.[160] The main difficulty, especially in patients with poor wound healing and poor surrounding soft tissue, is the differentiation between colonizing wound flora and causative pathogens of the device-associated infection. This should be taken into account because the proportion of exogenous infection is higher than in PJI. Therefore it is crucial to explore areas with the most florid tissue inflammation and to perform biopsies in close proximity to the device. The samples should be labeled with the anatomic localization. In the case of infections with chronic low-grade symptoms manifesting at a delayed or late time point, histopathologic examination should be added in parallel. This investigation is helpful in differentiating contamination of the biopsy specimens from true culture-positive results, in particular when low-virulence bacteria of the skin flora are involved and no inflammation is seen at histopathologic examination. If anaerobes are potentially involved, special media and a rapid transport from the operating room to the microbiology laboratory should be organized in order to increase the culture sensitivity.[170] Anaerobes should be suspected in the presence of dead spaces, hematoma, and areas of tissue or bone necrosis. In the case of removal of the hardware or parts of it, cultures in enrichment broth can be performed, although there is a high risk of contamination. Sonication of removed devices may increase the sensitivity of the culture. Comparative data in patients with internal fixation devices are lacking.

Imaging

Conventional radiographs after implantation, in particular when performed in serial follow-ups, are helpful to estimate bone healing, formation of a nonunion or sequestration, implant loosening, bone loss around screws, and migration of devices. However, there are no specific signs indicating infection. Therefore, additional parameters for infection are necessary for infection diagnosis. This is also true when early device loosening is detected. Ultrasound may reveal fluid collection in the proximity of a device and help guide puncture for microbiologic sampling. However, fluid collection is mainly seen in infections with acute symptoms. Therefore, for rapid and correct diagnosis, open surgery is more appropriate than fluid sampling. CT is helpful to estimate the extent of inflamed tissue and allows the detection of bone necrosis. Similar to conventional radiographs, serial CT scans can help in estimating the success of treatment by enabling evaluation of bone healing. Nuclear medicine imaging modalities may be helpful in estimating bone viability and the presence of sequestra in posttraumatic osteomyelitis,[171] but are not routinely used for the detection of internal fixation device infections. Their sensitivity and specificities have as not been investigated in large trials, and the costs are considerable. When these modalities are used, it is critical to discuss beforehand which nuclear technique (e.g., three-phase bone scan with SPECT-CT, white blood cell scintigraphy with SPECT-CT, FDG-PET/CT) should be used to answer a specific clinical question.[171]

Treatment Concepts

General Aspects

It is essential to establish the diagnosis of implant-associated infections early. Treatment goals are fracture consolidation and prevention of chronic osteomyelitis. The longer the disease duration, the more established the biofilm formation becomes and the less likely the implant can be retained. Stable hardware can be maintained in a patient without uncontrolled sepsis who has no signs of chronic osteomyelitis. The cure rate in such patients is between 68% and 100%,[36,172,173] provided that the fracture is stable. Clinical experience and data from animal studies suggest that stable fractures are less susceptible to infection than unstable bone components.[174–176] Therefore it is important to stabilize the fracture, even in the presence of an infection. This again requires a decision to retain or exchange the fixation device when infection is diagnosed. In addition to the biofilm age, the likelihood of the fracture achieving union before implant fatigue failure must be considered. If an infected implant is retained, antimicrobial suppression is required until bone union has occurred. Whether or not the device must be removed after bone consolidation also depends on the duration of infection before treatment. In the case of early infection or acute hematogenous infection after an uneventful postoperative period, rapid diagnosis and immediate surgical and antimicrobial treatment improve the outcome. The cure rate of early staphylococcal implant-associated infections treated with a fluoroquinolone-rifampin combination was shown to be high.[36] Hence, in these cases the implant does not have to be removed after consolidation. In contrast, in patients with delayed detection of infection, the biofilm may persist on the implant. Therefore all foreign material should be removed after bone healing. Antimicrobial therapy can be stopped shortly thereafter (i.e., within 1 week).

Systemic Antimicrobial Therapy

Principles of intravenous and oral antimicrobial treatment are not different in PJI and internal fixation–associated infection (see Table 105.2). However, there are no recommendations, nor are there comparative studies defining the length of treatment. In the case of early or acute hematogenous infection after an uneventful postoperative period, we propose 3 months of antimicrobial therapy.[36] In the case of delayed presentation of infection, treatment duration depends on the surgical intervention and may be prolonged as long as the device is retained. Bone consolidation should be regularly evaluated and the device removed after fracture consolidation. Thus the treatment duration can be kept to the shortest possible time.

Local Antimicrobial Therapy

In open fractures, particularly in those with high bacterial contamination, the implantation of antibiotic-loaded beads or spacers to fill dead space is common practice.[177] Although an aminoglycoside (e.g., gentamicin, tobramycin) is the standard antibiotic in spacers, virtually any antimicrobial agent can be added to spacers and beads.[138,178] The rationale behind this procedure is to reduce the local bacterial load in poorly vascularized areas. Also, bead chains can be placed in difficult-to-reach bone areas. In open fracture, several studies have reported a reduction of infection rates when adjuvant antibiotic-loaded beads were used.[178–180] It should also be considered that there will be a selection of bacteria with emerging resistance toward the antibiotics incorporated in beads and spacers.[181] Because these materials are foreign bodies, adherence of bacteria can occur.[182] Although antibiotics are released locally, uncommonly they may have systemic unwanted effects (e.g., nephrotoxicity of gentamicin).[183] Taken together, it is judicious to rapidly reduce the dead space and local bacterial load in a contaminated open fracture. Nevertheless, antibiotic-loaded beads and spacers are foreign bodies and should be removed within a short period of time. Removal is not necessary when beads constructed from bioabsorbable material are used.[184] Their use may result in significant leakage, making the clinical interpretation of wound oozing difficult (i.e., leakage from dissolving beads vs. infection). Of note, it should be considered that a muscle flap likely contributes its part to local antimicrobial defense via excellent vascularization and penetration into the tissue. Rapid closure of the wound is essential to hinder the penetration of skin flora into the wound.

Surgical Interventions

It is important to note that patients with implant-associated infections can benefit from rapid referral to specialized centers. Before surgery, the following factors must be assessed: viability of the soft tissue and bone, bone stability, fracture healing, implant stability, duration of the infection, and magnitude of the soft tissue defect.[166] The soft tissue envelope must be well vascularized and intact to provide systemic antimicrobial agents and immune cells to the infected area. As a rule, stability of bone fragments is required for union. In patients with unstable devices, there is neither bone consolidation nor healing of infection. Therefore, such implants should be removed and replaced with either a new internal fixation device (plate or intramedullary nail) or external fixation. External fixation is preferred in cases involving difficult-to-treat microorganisms (e.g., fungi or multiresistant microorganisms). The majority of early infections can be treated with débridement and implant retention. This is also true for patients with acute symptoms after an uneventful postoperative course. Débridement includes diagnostic biopsy sampling and meticulous removal of all necrotic tissue including dead bone, abscess membranes, and granulation tissue. The first intervention is generally the most important. In case of extensive tissue necrosis or hematoma formation, more than one intervention may be necessary—although the more thorough the first intervention, the fewer additional débridements are required. In nonearly infections, the decision to retain or to remove the implant depends on multiple factors, also because biofilm formation occurs on a time-dependent continuum. In patients with a delayed infection presentation, the same procedure as for early infection may applied, although with a different antimicrobial approach (see earlier). Conceivably, shorter disease duration implies a better prognosis. In patients with a long disease duration, the implant can generally not be retained. In patients with significant skin and soft tissue defects (a priori or as a consequence of meticulous débridement), the procedure should be combined with plastic and reconstructive surgery. Uncovered soft tissue defects or delayed wound healing may result in exogenous superinfection, which is often polymicrobial. The duration of both hospitalization and antimicrobial treatment is commonly long in patients having superinfections. Important to note, the development of superinfection is not hindered, but likely enhanced, when the wound is covered with a vacuum-assisted closure device.[164]

Plate-Associated Osteomyelitis

Internal fixation with a plate may lead to a devascularized area at the interphase between plate and bone. In the case of a subcutaneous position of the plate (e.g., tibial fracture), clinical diagnosis is obvious. With rapid diagnosis, débridement with implant retention and antibiotic treatment can be performed. If the plate is in a submuscular or subfascial position (e.g., femur fracture), diagnosis is often delayed, leading to instability of the infected nonunion. After removal of plates and screws because of infection, there is usually a layer of dead cortical bone under the plate. It can be shaved off with an osteotome. The implant has to be exchanged or, alternatively, replaced by external fixation.

Intramedullary Nail–Associated Osteomyelitis

According to experimental data, medullary nailing leads to necrosis in the central part of the cortex.[185] If diagnosis is delayed, infected nonunion requires the exchange of the implant. In these cases, bioabsorbable antimicrobial-impregnated beads can be inserted into the canal.[186] A multidisciplinary team should decide for each patient whether an infected nonunion can be treated with a single-stage protocol[184] or whether a two-stage protocol including external fixation is the better option.

Pin-Tract Infection

Local inflammation surrounding fixation pins is frequent, mainly due to heat necrosis caused by drilling at excessive speed and power. Extension of infection to the bone is less frequent. Pin infection should be rapidly treated with local cleaning and oral antibiotics. According to a Cochrane review, no specific pin-site care was better than any other for reducing the risk of infection.[187] If deep bone infection occurs, pins will loosen. The reported incidence of pin-tract infection was 11%, lowest for ring (4%) and highest for hybrid fixators (20%).[188] With established pin-site bone infection, a ring sequestrum will be formed. Surgical treatment

of such infections requires removing the involved pins, excising the ring sequestrum, and administering a short course of antibiotics. If bone fragments are not yet stable, new pins should be inserted at a distant site.

PREVENTION IN ORTHOPEDIC SURGERY

Perioperative Antimicrobial Prophylaxis

Arthroplasty and Closed Fractures

Timely correct antimicrobial prophylaxis reduces postoperative infections.[189–191,192] The Surgical Infection Prevention Guideline Writers Workgroup has suggested the infusion of the first antimicrobial dose within 60 minutes before surgical incision.[193] Several studies observed even lower infection rates when antibiotic prophylaxis was administered within 30 minutes before incision.[190,194,195] However, a recently published controlled trial randomized 5580 patients (39% of them in a trauma unit) for two different prophylaxis time points.[196] The median administration times before incision were 42 (interquartile range [IQR], 30–55) versus 16 (IQR, 10–25) minutes, and the overall rate of surgical site infections was 5% in both groups. In view of surgical site infections in patients with orthopedic implants, a follow-up of only 30 days is a limitation of this trial.

Most studies investigating the prophylactic effect of antibiotic-impregnated bone cement in elective orthopedic surgery have failed to demonstrate significant differences because of the small numbers of patients.[190] However, a study including 43,149 primary and revision knee arthroplasties (Finnish Arthroplasty Register) was able to show that the lack of antibiotic-impregnated cement increases the risk for reoperation because of infection. Cases in which patients received only intravenous prophylaxis were compared with those in which patients received combined antibiotic prophylaxis (hazard ratio [HR], 1.42 [95% CI, 1.08–1.88] for primary arthroplasty; HR, 2.12 [95% CI, 1.14–3.92] for revision arthroplasty).[51]

Intravenous antimicrobial prophylaxis should be stopped after the end of surgery. Continuation does not further reduce infection rates but may increase the incidence of resistant pathogens in subsequent nosocomial infections.[197–198,199]

Compounds for antimicrobial prophylaxis are usually selected according to local epidemiology, national guidelines, and in-house practices. Most centers use first- or second-generation cephalosporins. Dual antibiotic prophylaxis (i.e., cefazolin plus vancomycin) failed to prove superiority in reducing the overall rate of surgical site infections in comparison with cefazolin monotherapy.[200] Nevertheless, if the local epidemiology points toward high MRSA or multiresistant gram-negative colonization rates, or both, the compounds used for antimicrobial prophylaxis may be adapted accordingly, based on the recommendations of local hospital infection control specialists.

In case of suspected or definite orthopedic implant–associated infections, there are additional aspects regarding the timing of antimicrobial prophylaxis. Obtaining biopsy specimens after antimicrobial agents have reached significant tissue levels decreases the sensitivity of microbiologic culture.[201] The difference in sensitivity may not be critical in chronic infections, because bacteria can be cultured from necrotic bone.[201] Preferentially, samples should be obtained just before administration of antimicrobial prophylaxis. However, when surgery is performed during ischemia (e.g., total knee arthroplasty), antibiotic prophylaxis is administered before the tourniquet is inflated, potentially influencing microbiologic results. Still, a clinical trial analyzing whether antibiotic prophylaxis during elective knee arthroplasty should be administered before tourniquet inflation or can be delayed until just before tourniquet deflation found similar low deep-tissue infection rates in both groups.[202] Thus, prophylactic antibiotics can be delayed until tourniquet deflation, thereby avoiding antibiotic carryover during sampling for microbiologic evaluation.

Open Fractures

Open fractures are at increased risk for infection (see Table 105.3). Therefore, emergency surgery with antibiotic preemptive therapy (e.g., first-generation cephalosporins for up to 24 hours) is necessary. For type I and II fractures, the same compounds used for closed fractures are indicated. In cases of massive exogenous contamination (type III open fractures), certain experts recommend antibiotics that are more active against anaerobes or gram-negatives (e.g., ampicillin-sulbactam or piperacillin-tazobactam or flucloxacillin plus an aminoglycoside).[203] However, these recommendations are based on expert opinion and observational studies, and most cited data in the literature are at least 30 years old.[204]

In type IIIB and IIIC fractures, preemptive antimicrobial therapy is recommended. Similar to the lack of data regarding the optimal compound, the optimal duration is unknown. In previous publications, a period of 10 days has been reported.[205,206] Dellinger and colleagues[189] compared in a double-blind prospective trial 1 day versus 5 days of preemptive cephalosporin treatment in patients with open extremity fractures. The rates of postoperative fracture site infections were similar. Similarly, in a retrospective case-control study, Dunkel and colleagues[207] found no difference in subsequent infection rates when a 1-day course of antibiotics was compared with prolonged treatment, even for grade III open fractures. We recommend a 1-day (or a maximum 3-day) preemptive therapy course with ampicillin-sulbactam or amoxicillin–clavulanic acid in patients with grade III open fractures. Early administration after trauma appears to be more important than the duration of preemptive therapy.[208] Closure of the wound should be strived for as soon as soft tissue conditions allow doing so in cases of open fractures. Also, rapid stabilization of the fracture is necessary. In type III fractures, initial external fixation should be preferred for a short period because of the high risk of infection with intramedullary nailing. Hence, adequate surgical procedures reduce the rate of posttraumatic infections, illustrating the importance of an interdisciplinary approach.

Prevention of Hematogenous Infection

Because implants are highly susceptible to bacterial adherence, the risk of hematogenous infection remains as long as the device is implanted.[40–43] Accordingly, means to prevent hematogenous infection are limited. Patients should be informed about the risk and reminded to rapidly contact a physician when signs of infection occur, irrespective of localization. It is important to treat obvious infections (e.g., pneumonia, skin and soft tissue infections, urinary tract infections) rapidly in order to prevent bacteremia.

A further approach is the application of hygiene measures to potential sources of bacteremia. These include *S. aureus* decolonization and dental hygiene procedures. In a double-blind, placebo-controlled, randomized study including patients undergoing elective orthopedic surgery, eradication of *S. aureus* nasal carriage with mupirocin was not effective in reducing surgical site infections. However, the rate of hematogenous *S. aureus* infections was five times lower in the mupirocin group.[209] Similarly, orodental hygiene and regular dental treatment can be recommended because these might result in reduction of risk of hematogenous PJI.[210,211] In contrast, antibiotic prophylaxis to reduce the risk of hematogenous seeding and joint contamination during dental surgery is unnecessary.[211–214] This is true for both low- and high-risk dental procedures.[210] Similarly, genitourinary procedures are not risk factors for subsequent PJI, and consequently antibiotic prophylaxis is not required.[215]

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The complete reference list is available online at Expert Consult.

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L Diseases of the Reproductive Organs and Sexually Transmitted Diseases

106 Genital Skin and Mucous Membrane Lesions

Michael H. Augenbraun

SHORT VIEW SUMMARY

Definition
- Infectious genital skin and mucous membrane lesions cover a wide spectrum of pathologic etiologies and clinical presentations, mostly manifesting as inflammatory reactions or defects in the epithelium of the genital tract in men and women.

Epidemiology
- Infectious genital skin and mucous membrane lesions are seen globally without seasonality.
- These lesions occur primarily in sexually active individuals.
- Most are due to sexually transmitted infections, but neoplastic and noninfectious inflammatory processes should be considered, especially in older individuals.
- Incubation periods may vary according to etiology: for human papillomavirus, it may potentially be weeks, months, or years after exposure; for primary syphilis, it may be weeks to months; for herpes simplex virus (HSV) outbreaks, it may be years.
- Disease may be modified in populations that are immunocompromised.
- Some conditions are currently being seen more frequently in men who have sex with men (i.e., early-stage syphilis, lymphogranuloma venereum [LGV]).

Microbiology
- Bacteria: *Treponema pallidum* (spirochete), *Haemophilus ducreyi* (gram-negative diplococcus), *Chlamydia trachomatis* L serovars (obligate intracellular pathogen), *Klebsiella granulomatis*/donovanosis (gram-negative rod)
- Viruses: HSV, molluscum contagiosum virus, human papillomavirus
- Fungi: *Candida albicans*

Diagnosis
- Clinical assessment alone may be misleading.
- Laboratory examination using microscopy and serologic testing is often helpful.
- Gram staining and light microscopy help to identify *H. ducreyi* and *Candida* spp.
- Darkfield microscopy is used to identify *Treponema pallidum*.
- Serology helps to diagnose *T. pallidum* and HSV.
- Nucleic acid amplification tests (NAATs) and less often cell culture testing are used to diagnose HSV.
- NAATs are used to identify *C. trachomatis*.

Therapy
- Therapy is best chosen based on the likely or specific etiologic agent.
- Syphilis is treated with penicillin and tetracyclines.
- HSV infection is treated with acyclovir, valacyclovir, or famciclovir.
- *C. trachomatis* causing LGV should be treated with tetracyclines.

Prevention
- Safe sex
- Partner contact tracing
- Preemptive treatment based on contact and risk

Genital lesions are of uncertain historical pedigree. Ancient Chinese medical writings dating back to 2500 BCE appear to have alluded to a "corroding ulcer" of the genitals developing a few days after coitus.[1] There are references throughout the Old Testament to genital pathology that may have been infectious in nature. Ancient Greek, Roman, and Arabic medical texts also suggest a familiarity with acute genital infections, but the descriptions are difficult to associate with any specific clinical syndrome recognized today.[2,3]

Although genital lesions originate from a wide range of infectious and noninfectious processes, they most commonly result from sexually transmitted or venereal infections (Table 106.1).[4,5,6,7] Other pathologic processes including chemical and mechanical trauma, neoplasia, and immunologic phenomena, can cause genital lesions (Table 106.2). The term *venereal,* as it relates to disease, dates to the 15th century. Its root comes from the Latin *venereus* or *venus,* meaning "from sexual love or desire." In the United States the most common causes of sexually transmitted genital lesions are herpes simplex virus (HSV) type 2, *Treponema pallidum* (syphilis), and human papillomavirus (HPV).[8]

Infectious genital lesions are unique in a number of ways compared with other infectious processes. Most are communicable and are not only a clinical concern but also a public health concern. Infectious genital lesions can harbor more than one pathogen at a time, making proper diagnosis and management a challenge.[9,10] The morphologic appearance of the lesion can differ widely from one clinical presentation to another, even when the causative organism is the same. The unpredictable nature of clinical presentation of the lesion can make a purely clinical diagnosis unreliable.[11,12,13] Inflammatory epithelial defects characteristic of these pathologies appear to enhance the transmission of other diseases, most importantly human immunodeficiency virus (HIV).[14,15–20]

This chapter focuses on the broad issues relevant to the assessment and management of genital lesions. For in-depth discussions of individual pathogens, readers are directed to the chapters that address those topics.

HISTORY OF PRESENTATION

Individuals who present with a new genital lesion and who report recent sexual activity, particularly activity with a new partner or someone with a suspected genital infection, are likely to have a sexually transmitted infection. Certain clinical circumstances suggest nonsexually transmitted pathology such as trauma, chemical irritation, or allergic hypersensitivity. A lesion that occurs proximate to sexual exposure (i.e., within hours to 1 or 2 days) may be too early to account for the incubation period of most infectious pathologies. In the case of a lesion with rapid onset, the nature of the sexual activity, a topic often left unexplored by the clinician and patient, may suggest trauma.[21,22] Traumatic genital lesions

TABLE 106.1 Infectious Causes of Genital Lesions

Sexually Transmitted Infections
Syphilis
Primary (chancre)
Secondary (condyloma latum)
Herpes simplex virus types 1 and 2
Chancroid *(Haemophilus ducreyi)*
Lymphogranuloma venereum
Granuloma inguinale (donovanosis)
Human papillomavirus
Sarcoptes scabiei
Molluscum contagiosum
Nonsexually Transmitted Infections
Folliculitis
Tuberculosis
Tularemia
Histoplasmosis
Candida (balanitis or vaginitis)
Amebiasis

TABLE 106.2 Nonvenereal Causes of Genital Lesions

Trauma
Malignancies (e.g., squamous cell carcinoma)
Behçet syndrome
Lipschütz vulvar ulcers
Peyronie disease
Fixed drug eruption
Eczema
Psoriasis
Inflammatory bowel disease
Contact dermatitis
Lichen planus
Hidradenitis suppurativa
Postinflammatory hypopigmentation
Aphthous ulcers (associated with human immunodeficiency virus)

may result from sexual assault, questions about which are also often avoided.[23,24] Recurrent lesions in someone who uses or whose partner uses latex condoms may be attributable to a latex allergy, although allergy typically results in more generalized edema and erythema of the genitals rather than a focal ulcer or papular lesion.[25] The geographic prevalence of disease may be an important factor to consider when assessing a genital lesion in a traveler.

A history of recurrent genital lesions, with or without dysesthesias preceding the development of lesions, usually suggests an infection with HSV. HSV-2 and, less commonly, HSV-1 cause a genital ulcer that is characterized by repeated symptomatic or often subclinical outbreaks separated by variable periods of quiescence during which the virus is localized to the dorsal root ganglia of adjacent sensory nerves. A variety of factors are postulated to contribute to viral shedding (which may or may not be associated with a genital ulcer) including immunosuppression, other intercurrent illnesses, sun exposure, and menses.[26,27] Data suggest that initiation of highly active antiretroviral therapy in HIV-seropositive patients may reactivate HSV-2 shedding.[28]

Host factors can be important historical determinants of etiology of a genital lesion. Patients with preexistent psoriasis or eczema or other noninfectious dermatitides may have a genital lesion related to the underlying dermatologic pathology. Nongenital autoimmune conditions may suggest an autoimmune cause for genital lesions such as lichen planus.[29] Recent history of medication use such as tetracyclines or antineoplastics in a patient presenting with a new genital lesion can prompt consideration of a fixed drug eruption. In these cases, lesions may be characterized by pigmentation or superficial ulceration.[30,31] Candidal balanitis in men has been associated with immunosuppression, contact with a partner who has vaginal candidiasis, and diabetes.[32–34] Vulvovaginal candidiasis is an extremely common problem that may manifest as focal genital lesions.[35] Although it may be more common in women with underlying immunosuppression (e.g., diabetes mellitus, HIV infection, long-term steroid use), vulvovaginal candidiasis occurs most frequently in women without such risk factors.[35,36] Autoimmune diseases such as acute reactive arthritis, Crohn disease, or Behçet syndrome may be associated with genital lesions.[37–39] The spectrum of typical and atypical genital lesions associated with HIV infection is broad and includes Kaposi sarcoma, giant condyloma acuminatum, chronic nonhealing HSV, typical HSV, syphilis, and chancroid.[40,41,42,43] This reflects both the common occurrence of coinfection with other sexually transmitted diseases and a propensity for HIV immunosuppression to modulate other conditions.

CLINICAL MANIFESTATIONS

Location

In men, lesions associated with infectious or noninfectious processes may be found on or under the prepuce, around the coronal sulcus, on the shaft of the penis, on the scrotum, on the perianal tissue, or on the inner thighs. In women, sites of involvement are equally varied. Genital lesions can appear on the mons pubis, labia, fourchette, cervix, inner thighs, perianal tissue, or anywhere in the vagina. As a result of orogenital sex, pathogens such as HSV and *T. pallidum* can also cause orolabial lesions. Anyone who engages in receptive anal intercourse is at risk for developing an infectious lesion in the perirectal area, the rectum, or the anus. Lesions of chancroid can be disseminated distant from the genitalia and the original site of infection by a process of autoinoculation.[44,45] Data suggest that as venereal chancroid rates decline, there may be an increase in nongenital yawslike cutaneous presentations in children.[46] In secondary syphilis, spirochetemia causes lesions, sometimes widely dispersed from the genitalia, that morphologically range from the classic papulosquamous rash of the palms and soles to the moist, raised lesions of condylomata lata (genitals) or mucous patches (orolabial area). *Neisseria gonorrhoeae,* a pathogen not commonly associated with genital lesions, may disseminate and cause tender, necrotic pustules, primarily on the distal extremities as part of an arthritis-dermatitis syndrome.[47] Lesions associated with scabies infestation are common in the genital region as well as intertriginous areas elsewhere including, but not limited to, the axillary folds and the interdigital spaces. Genital edema can occur after any local inflammatory process.[48]

Pain, Dysesthesias, and Systemic Symptoms

The lesions of syphilis, lymphogranuloma venereum (LGV), scabies, molluscum contagiosum, and HPV are ordinarily painless. Exceptions are noted in the medical literature.[49] Herpetic lesions are usually painful, although they may not be noticed until the clinician examines the patient and palpates or abrades the lesion. If HSV lesions are adjacent to or within the urethra, the patient can experience dysuria. Sometimes pain or other dysesthesias including pruritus may precede the development of a clinically recognizable HSV lesion, particularly during episodes of disease recurrence.[50,51] These so-called prodromal symptoms are usually milder than symptoms experienced during a primary outbreak. They may be so characteristic that patients can be reliably instructed to begin antiviral medication before lesions erupt. Chancroid ulcers are typically painful. Genital lesions from immunologically mediated noninfectious causes such as Behçet syndrome, genital extensions of Crohn disease, aphthous ulcers, and vulvitis/vestibulitis may also be exquisitely tender. Granuloma inguinale (donovanosis), a genital ulcer disease seen primarily in the tropics, is caused by the bacillus *Klebsiella granulomatis.* Although the lesions of this disease are often large and destructive, pain is absent. Most patients with exophytic genital warts are asymptomatic; a few may report pain or pruritus.

Pruritus is common with fungal infection and with ectoparasitic infestations such as scabies or lice. The pruritus associated with scabies is often described as intense and worse at night. Although pruritus may be experienced by individuals with HSV or syphilis, it is not characteristic of these conditions. Fever is occasionally seen with secondary syphilis and with primary HSV infection but usually is absent.[51,52] Headaches, fatigue, myalgias, and malaise may also accompany these infections.

Lymphadenopathy

Inguinal lymphadenopathy is a nonspecific finding characteristic of inflammatory pathology almost anywhere in the groin or either lower

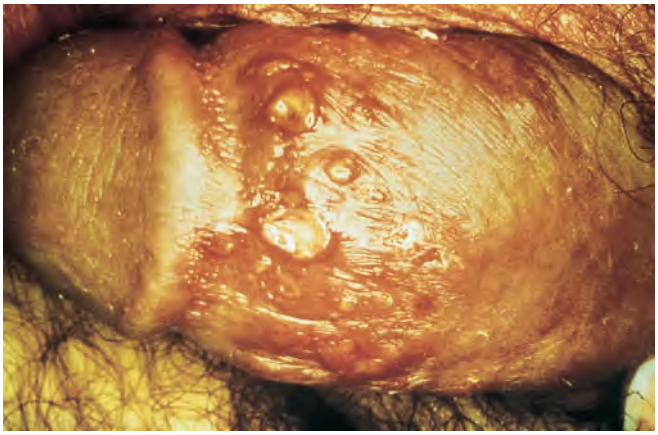

FIG. 106.1 Herpes simplex virus infection. Genital infection with herpes simplex virus.

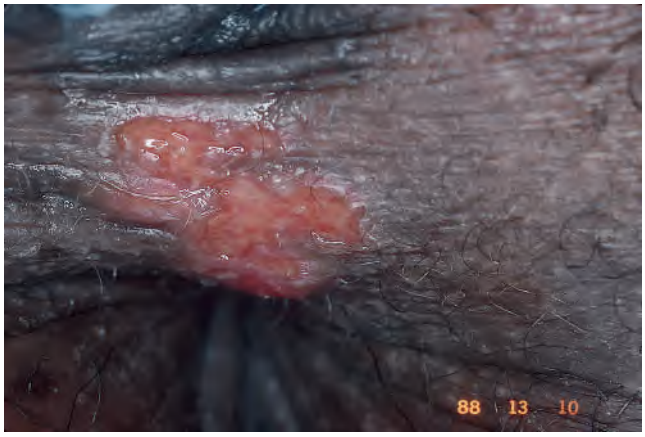

FIG. 106.2 Herpes simplex virus ulcer. An irregularly shaped herpes simplex virus ulcer.

extremity. It may also be a manifestation of systemic disease such as HIV infection, tuberculosis, or lymphoma. It often accompanies genital infection. Although the inguinal and femoral lymph nodes drain the genital region in both men and women, the inner segment of the vagina and the cervix drain into deep pelvic and perirectal lymph nodes. Anorectal lymph drainage patterns are also complex and depend on whether infection occurs above or below the dentate line (the mucocutaneous junction in the rectum). In either case, if pelvic lymph nodes are involved in inflammatory genital pathology, pelvic or rectal discomfort may be the most striking symptom.

Bilateral inguinal lymphadenopathy is typical in syphilis. Similar to the chancre of primary syphilis, it is usually painless. In secondary syphilis, as befitting a systemic process, lymphadenopathy distant from the genital area is common. Typically the inguinal, axillary, cervical, and epitrochlear nodes are involved.[52] Lymphadenopathy associated with a herpetic genital lesion is usually bilateral and, similar to the lesion, is tender. In HSV infection and in syphilis, lymphadenopathy persists for some time after resolution of the lesion.

LGV and chancroid are characterized by expansive, tender lymph nodes called *buboes*. These may be unilateral or bilateral. A central area of fluctuance often develops; if left untreated, it eventually spontaneously ruptures. Although drainage may be spontaneous, tenderness can become sufficiently severe to warrant intervention and drainage. Lymphadenitis is unusual in granuloma inguinale.

Lesion Morphology

Although the appearance of a genital lesion is not entirely specific, it can implicate an etiologic agent. HSV infections are characterized by vesicles that evolve into pustules and finally to shallow ulcers on an erythematous base (Fig. 106.1). Multiple lesions are common, and they may erupt in tightly grouped clusters. Sometimes the characteristic evolution of the lesion is not appreciated, and the patient or clinician simply observes tender ulcers that assume a wide variety of shapes and sizes because of confluence of evolving vesicles and pustules (Fig. 106.2). In a primary outbreak, lesions can reach sizes greater than 1 to 2 cm in diameter (Fig. 106.3). Immunocompromised patients such as transplant recipients, patients taking immunosuppressive drugs, and patients infected with HIV can also experience extensive herpetic ulceration of the genitals in the setting of either a primary outbreak or a recurrence.[43,53,54] At the other end of the spectrum, a substantial proportion of individuals fail to recognize HSV outbreaks because of mild or absent symptoms.[55] When instructed carefully about these types of outbreaks, most of these individuals can recognize disease.[56]

Syphilitic chancres are typically solitary, although they may rarely occur in pairs. They are round and 1 to 2 cm in diameter, with clean margins that are indurated on palpation (Fig. 106.4). The ulcer base usually lacks exudate but occasionally becomes superinfected with other bacteria.

The lesions of secondary syphilis are not chancre-like. They may start anywhere as fine macular lesions that evolve into pigmented papules,

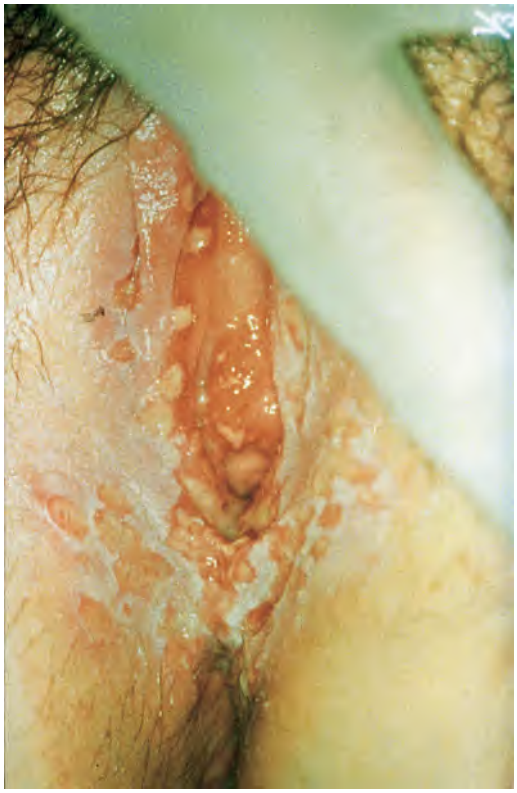

FIG. 106.3 Primary herpes simplex infection. Severe primary herpes simplex virus infection.

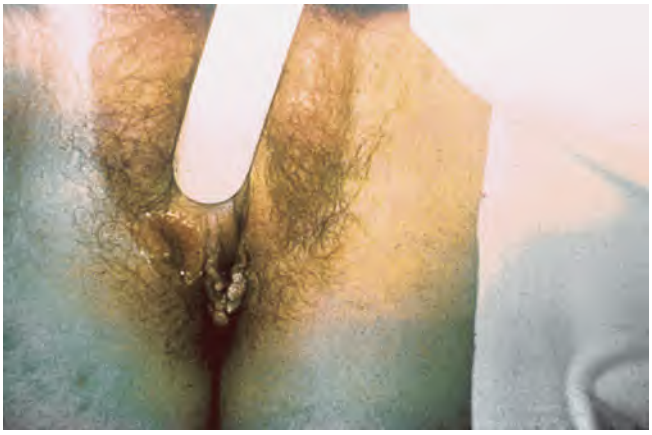

FIG. 106.4 Primary syphilis. Chancre of primary syphilis.

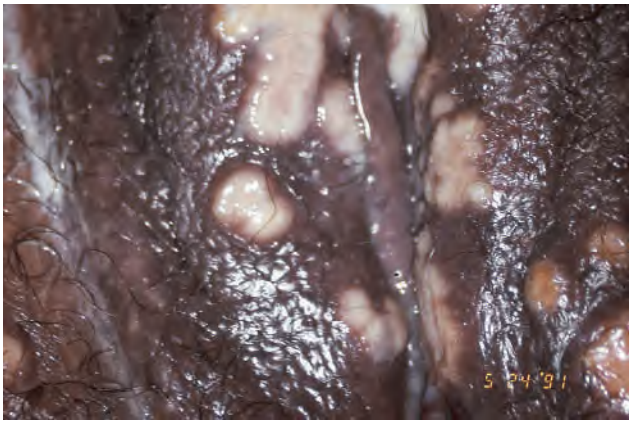

FIG. 106.5 Secondary syphilis. Condylomata lata of secondary syphilis.

often with a fine, circumferential scale. In warm, moist areas such as the buttocks and genitals, unique lesions of secondary syphilis, known as condylomata lata, develop (Fig. 106.5). These are raised, moist nodules or plaques that are teeming with treponemes. They are highly infectious.

Chancroid lesions are similar in size to syphilitic chancres, but their edges are ragged and undermined (Fig. 106.6). The ulcer base is necrotic with a purulent exudate. Compared with the lesions of syphilis, induration of chancroid lesions tends to be less prominent, accounting for the designation of these ulcers as "soft chancres" *(ulcus molle, chancre mou)*. Despite the obvious tissue damage, adjacent inflammation is absent. Single lesions are the norm, but multiple lesions may be seen. As noted before, chancroid lesions, similar to HSV ulcers and in contrast to syphilis chancres, are tender.

The lesions of granuloma inguinale start as firm subcutaneous nodules or papules that eventually ulcerate. Typically, this ulcerative process becomes hypertrophic and bleeds easily (Fig. 106.7).[57] Local tissue destruction may be extensive. Swelling of the vulva and prepuce (causing phimosis) is common. Variants include deeply necrotic ulcers and dry, so-called cicatricial lesions that consist primarily of fibrotic tissue. Lesions occasionally are confused with squamous cell carcinoma.[58]

LGV is one of several sexually transmitted diseases caused by *Chlamydia trachomatis* and is attributable specifically to serovars L1, L2, and L3. At its earliest stage, LGV may cause a small papule or rarely a HSV-like ulcer.[59,60] This is usually asymptomatic and resolves before recognition.[61] The patient with LGV then comes to medical attention with tender inguinal lymphadenopathy as the primary process of concern. If the source of exposure is via anal intercourse, clinical manifestations may be more difficult to discern. Deep pelvic lymph nodes are commonly involved, and patients present with proctitis or proctocolitis.

Clinically visible lesions of HPV are typically caused by viral types with low oncogenic potential (i.e., types 6 and 11).[62] Most HPV infections are asymptomatic. Lesions can run the gamut from flat or relatively inconspicuous papules to verrucous, pedunculated, or large cauliflower-like masses—all referred to as *condylomata acuminata* (Fig. 106.8). Whatever the configuration, these lesions are clinically characteristic and unlikely to be confused with lesions of other etiologies. Certain HPV types (e.g., 16, 18, 31, and 33) have oncogenic potential both on moist mucosal surfaces such as ectocervix and, less commonly, on keratinized epithelium characteristic of the external genitalia. The dysplastic cytologic changes they induce are collectively referred to as squamous intraepithelial neoplasia and may be benign or malignant. Squamous cell carcinoma of the cervix, vagina, vulva, penis, or anus arises from previous HPV infection. HPV-associated carcinoma in situ on keratinized epithelium may manifest as multiple papular lesions, referred to as bowenoid papulosis (Fig. 106.9) or, when it occurs as a single plaque, as Bowen disease. Erythroplasia of Queyrat is a variant of this process that involves the glans of the penis.

The poxvirus molluscum contagiosum virus (MCV) causes benign, wartlike lesions (Fig. 106.10). Spread can be sexual or through nonsexual

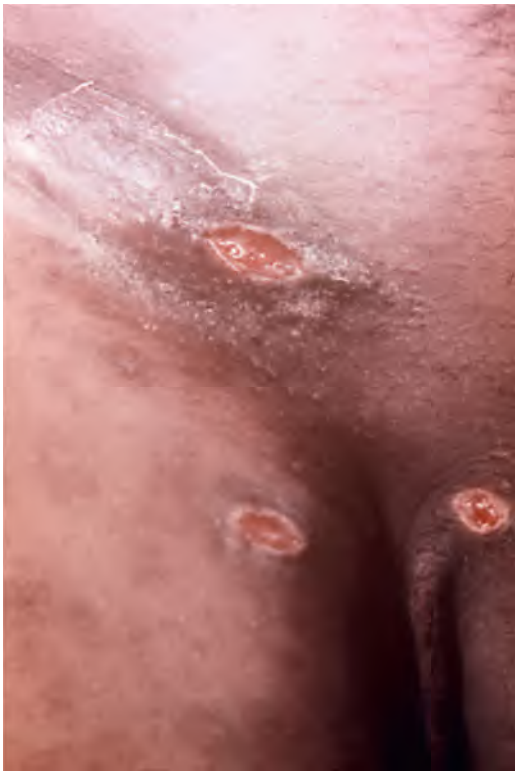

FIG. 106.6 Chancroid *(Haemophilus ducreyi)*. Lesions involving the penis and the inguinal and femoral lymph nodes.

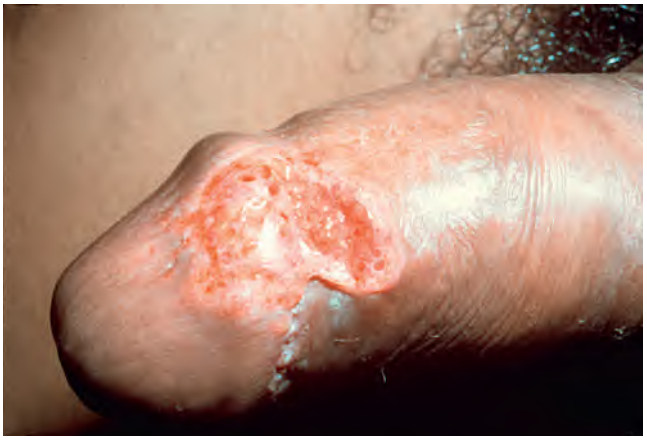

FIG. 106.7 Granuloma inguinale. Tissue smear was positive for Donovan bodies.

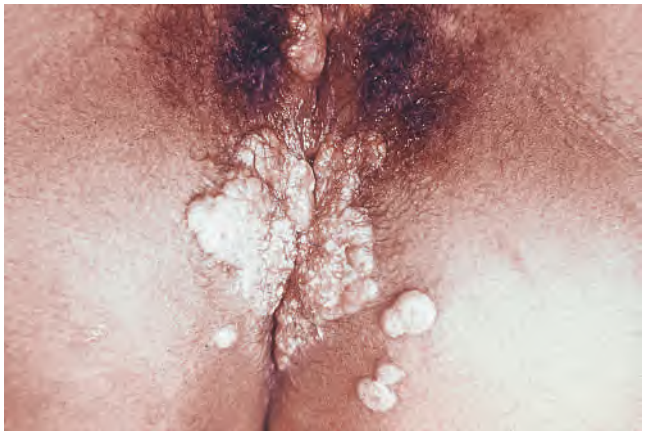

FIG. 106.8 Human papillomavirus. Genital human papillomavirus lesions.

contact in children. Lesions are small, 3 to 5 mm in diameter, multiple, and clustered in the genital or inguinal areas, perineum, or inner thighs in adults and are almost always painless. They appear pearly with an area of central umbilication, which often can be appreciated only on very close inspection. Lesions of scabies infestation range from papules to nodules with a surrounding crust (Fig. 106.11). With scratching, these lesions are often modified by excoriations or lichenification.

The use of systemic or topical antimicrobial agents before clinical evaluation can have a dramatic effect on lesion morphology in any of these various cases.

Duration

Without therapy, HSV ulcers resolve within 3 weeks in cases of primary infection. Recurrences resolve in 5 to 12 days. Except for some postinflammatory hypopigmentation, there is little scarring. Lesions that heal within days after an outbreak in the absence of therapy are probably not herpetic in nature. However, lesions proven to be herpetic and persisting for longer than 3 to 4 weeks raise the possibility of underlying immunosuppression. Syphilitic chancres and condylomata lata also resolve without therapy, usually between 3 and 12 weeks and usually without much scarring. Without therapy, the lesions of chancroid and donovanosis are slowly destructive. Scarring is typical in both of these situations. Lesions caused by HPV or MCV may persist unchanged for a prolonged time, or they may be characterized by brief periods of clinical disease alternating with resolution. Molluscum contagiosum lesions may resolve on their own after several months but may persist in immunocompromised patients.

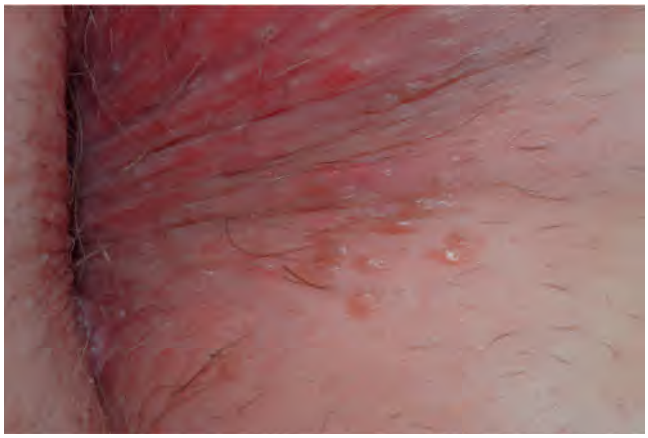

FIG. 106.9 Bowenoid papulosis.

EPIDEMIOLOGY

Understanding of the epidemiology of genital lesions has been hampered by inconsistent access to diagnostic tools in many parts of the world. The probability of a given cause of a genital lesion varies depending on the region of the world in which the patient lives or acquires infection (Table 106.3).[63–66] Worldwide, HSV-2 is the most common cause of genital ulcer disease.[67,68]

Although previously a common cause of genital ulcer in the developing world, chancroid has become increasingly rare,[69,70] possibly related to widespread antibiotic use and incidental reduction in the reservoir or transmission, or both, of the pathogen. In the developed world, *Haemophilus ducreyi* is usually seen only in the context of focal urban outbreaks.[71,72]

In the absence of reliable serologic tests for HPV infection, it has been difficult to accurately determine the prevalence of this organism in different regions of the world. This assessment is further hampered by the asymptomatic nature of most infections. Despite these handicaps, some studies suggest that HPV may be one of the most common sexually transmitted infections in the United States.[73,74] Sometimes this infection results in the typical lesions of external genital warts known as condyloma acuminatum.[75] Although initially envisioned as a tool for preventing cervical infection and therefore avoiding the development of neoplasia, the HPV vaccine has also been associated with a decline in the prevalence of genital warts in several population-based studies.[75–78,79,80] This is not surprising, as two of the most common types of HPV, 6 and 11, cause the majority of condyloma acuminatum and are included in the currently available nonavalent vaccine. By directly immunizing vaccinees and

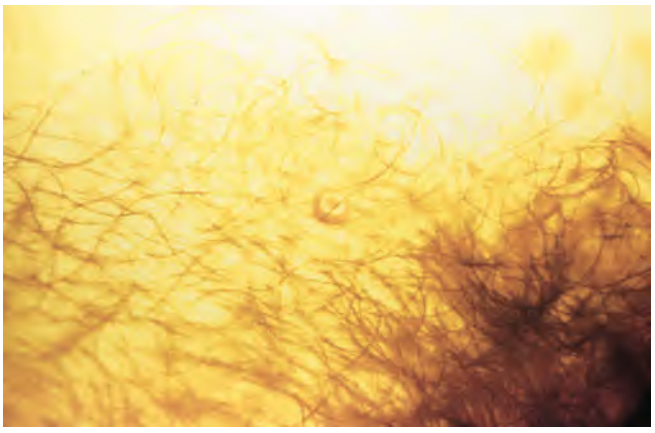

FIG. 106.10 Molluscum contagiosum. Lesion of molluscum contagiosum.

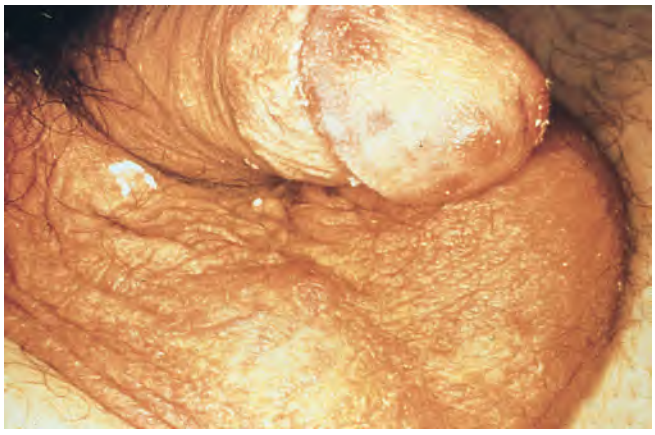

FIG. 106.11 Sarcoptes scabiei. Infestation with *S. scabiei.*

TABLE 106.3 Causes of Genital Ulcer Disease by Region (Percentage of Cases)

PATHOGEN	DAR ES SALAAM[4]	SOUTH AFRICA[61]	LOS ANGELES[5]	ST. LOUIS[5]	THAILAND[62]	MADAGASCAR[63]
Herpes simplex virus type 2	63	36	76	53	82	10
Haemophilus ducreyi	13	32	0	0	0	33
Treponema pallidum	2	20	0	13	0	29
>1 pathogen	10	9	0	2	2	—
Negative	21	22	24	32	16	32

where vaccine uptake has been substantial by creating significant herd immunity, the HPV vaccine may be the most effective way we currently have for controlling this common infection.

The incidence of syphilis in the United States declined so precipitously through the 1990s that the US Public Health Service embarked on an ambitious program to eliminate the disease from the country.[81] Despite these efforts, the incidence of early-stage syphilis, particularly among men who have sex with men and many of whom are also infected with HIV, has been increasing not only in the United States but also throughout the world.[82–86]

LGV occurs primarily in the tropics and subtropics.[61,87] Sporadic cases and outbreaks of LGV occur in the developed world, and the disease should be considered in travelers returning from endemic areas.[88,89] More recently, LGV outbreaks characterized by ulcerative proctitis have been noted among men who have sex with men in both Europe and North America.[90–93] Donovanosis is endemic in Papua New Guinea but has also been seen in southern Africa, parts of India, the Caribbean, and South America. It is infrequently seen in the United States.[57]

Genital Lesions in Patients With Human Immunodeficiency Virus

Although most HIV-infected patients with genital lesions manifest disease in a fashion similar to their nonimmunocompromised counterparts, it is clear that some patients, particularly patients with significant immunosuppression, experience more extensive and prolonged disease. Large, persistent, or progressive condylomata acuminata have been well described in this patient population.[94,95] In patients with HIV infection, the lesions of molluscum contagiosum can also vary in size and may number in the hundreds.[96,97] In this population, both primary and recurrent herpetic ulcers may progress to extend over large areas of the perineum.[43,98] The pain associated with such lesions can be so debilitating that it warrants hospitalization. HSV lesions in HIV-infected patients may persist well beyond the 2- to 3-week period ordinarily encountered in classic primary or recurrent disease. This finding may serve as an early sign of immunosuppression.[99–101] There has also been concern that HIV-infected patients are more likely to harbor HSV isolates that are resistant to commonly used antiviral agents.[102,103] The lesions of early-stage syphilis probably are not appreciably altered by HIV infection, although some data suggest that patients present more frequently than usual with multiple chancres. Clinical manifestations of secondary lesions may also develop before the resolution of the syphilitic chancre more commonly in HIV-infected individuals.[104,105,106] Rarely, aggressive forms of secondary syphilis have been reported in patients with HIV/acquired immunodeficiency syndrome.[107,108] Whether this truly reflects an altered presentation in this population remains unclear. Anecdotal reports of accelerated disease and failure of routine therapy have not been supported by prospective studies.[104]

Any break in the ordinarily protective barrier of the integument such as that caused by genital inflammatory lesions can serve as a conduit through which HIV is more efficiently transmitted from one sexual partner to another. Lesion exudate has been demonstrated to harbor virus.[109] There is additional concern that genital HSV-2 may increase local HIV replication, further enhancing the risk of transmission.[110] Syphilis, HSV, and chancroid infections have been associated with a greater likelihood of HIV infection in both retrospective and prospective studies.[111–114]

LABORATORY TESTING

Laboratory tests are critical to the diagnosis and proper management of genital lesions. As previously discussed, although specific pathogens can be linked to well-characterized clinical presentations, there is enough variation to ensure that clinicians relying on educated guesswork will be wrong in a significant number of cases. The following discussion is not meant to be exhaustive; for more details, reference should be made to the individual pathogens discussed elsewhere in the text.

A number of direct microscopic examinations can be performed on lesion exudate or a biopsy sample and can help make a diagnosis. Gram staining usually is not helpful in the evaluation of genital lesions. Lesion exudate is laden with nonpathogenic organisms common to genitourinary and perirectal microbiota. Under ideal circumstances, *H. ducreyi* appears as a gram-negative, slender rod or coccobacillus that aligns in a pattern referred to as "school of fish" (Fig. 106.12). Most clinicians and microbiologists are not sufficiently experienced to recognize this in the welter of other organisms typical of a lesion Gram stain, and its sensitivity and specificity are poor. *H. ducreyi* can be cultivated on special nutrient media using Mueller-Hinton–based chocolate agar, supplemented with 1% IsoVitaleX (Becton Dickinson, Franklin Lakes, NJ) and 3 μg/mL vancomycin to inhibit the growth of other organisms.[115] The rarity of this organism and the expense and limited shelf life of the media make isolation of *H. ducreyi* difficult and uncommon.

Light microscopy of syphilis chancre exudate is not useful. The spirochetes that cause syphilis do not take up standard stains well and are extremely thin. Darkfield microscopy of lesion exudate from either a chancre or condylomata lata can identify spirochetes. Incident light is angled obliquely at the stage by polarizing lenses and then reflected upward through the objective by microbes in the clinical specimen. Spirochetes appear as tightly coiled, white organisms spirally rotating against the black background of the microscopic field.[116] There are nonpathogenic treponemes, particularly in the oral cavity, which cannot be differentiated from *T. pallidum* by darkfield microscopy. In the appropriate clinical setting, a positive darkfield specimen is highly suggestive of syphilis. To perform a proper darkfield examination, ulcers must be cleaned with gauze and saline. Exudate from the lesion is then pressed against a glass slide. The specimen should not be contaminated with too much blood. A coverslip is then applied. Rapid examination of the specimen is essential because desiccation reduces the viability of organisms. Agar-based methods for the cultivation of *T. pallidum* are not routinely available. Direct fluorescent antibody testing of smears or tissue is available and, in contrast to darkfield microscopy, can differentiate between pathogenic and nonpathogenic treponemes.[117] Silver staining of biopsy material can identify spirochetes but is not commonly performed.

Serologic testing is the most commonly used method for the diagnosis of syphilitic genital lesions. The process requires two steps: a screening test that detects serum antibodies to nontreponemal antigens (e.g., rapid plasma reagin test, Venereal Disease Research Laboratory test, unheated serum reagin test), and then a confirmatory test that detects serum antibody to true treponemal antigens (e.g., fluorescent treponemal antibody absorption test, *T. pallidum* particle agglutination assay).[118] Early after the appearance of the syphilitic chancre, only the treponemal-specific test may be reactive. Repeat testing with the nontreponemal test should be considered at some time after the ulcer has formed. In rare situations, the nontreponemal test may be falsely nonreactive in secondary syphilis because of the blocking effect of excess antibody; this is known as the prozone phenomenon. In this situation, repeat testing should be performed on diluted serum specimens. Ordinarily the nontreponemal serologic test reaches its highest titer in secondary disease and declines with the onset of latency or with effective therapy. For the purpose of economy, enzyme immunoassay methodologies using

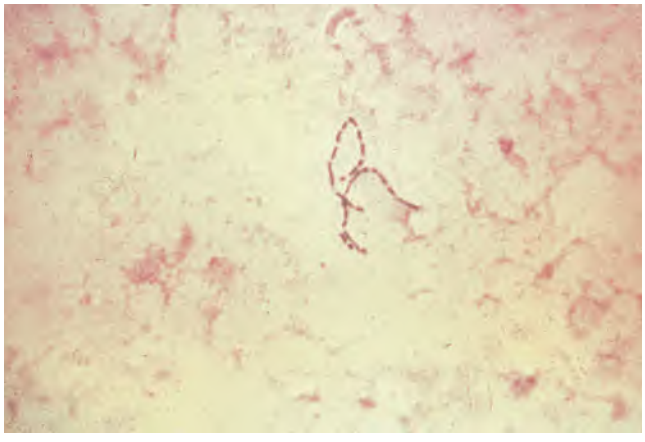

FIG. 106.12 Haemophilus ducreyi. Gram stain of *H. ducreyi.*

treponemal antigens have been introduced as screening tests. When reactive, these need to be confirmed by traditional nontreponemal specific tests. The use of this reverse algorithm has been shown to identify many more suspected cases of latent syphilis than the traditional testing algorithm.[119] The significance of a reactive enzyme immunoassay treponemal test unconfirmed by a nontreponemal test has not been clearly established.[120]

HSV-infected genital lesions can be identified by light microscopy using the Tzanck smear. In this procedure, epithelial cells are scraped from an ulcer base and stained with Wright-Giemsa stain. Multinucleated giant cells and intranuclear inclusions are characteristic of HSV infections. However, both the sensitivity and the specificity of the Tzanck smear are poor.[121] Nucleic acid amplification tests (NAATs), now recommended for HSV testing, are increasingly available and provide excellent sensitivity even in situations where culture may be negative.[122] When available, conventional cell culture also can provide a relatively rapid and accurate diagnosis, but culture has largely been replaced by NAATs. Most specimens from a genuine lesion of HSV demonstrate the pathognomonic cytopathic effect within 48 hours after collection. Fluorescein-conjugated type-specific monoclonal antibody can then be applied to these specimens for confirmation. Serologic tests for HSV antibodies are currently available and can distinguish between antibodies to viral glycoprotein G, which allows for distinction between HSV-1 and HSV-2.[123] Given the prevalent, chronic, and recurring nature of HSV genital infections, these tests are not typically used to establish the role of HSV as a cause of an acute genital lesion. Further modifications now allow these tests to be performed rapidly in the office or clinic.[124]

Klebsiella granulomatis, the cause of granuloma inguinale, or donovanosis, can be identified by staining scrapings of a lesion base with the Wright-Giemsa stain (Fig. 106.13). Surface cells alone may not harbor the organism, so biopsy is often necessary. Clusters of blue rods, with prominent polar granules and surrounded by pink capsules, are seen within infected epithelial cells and are known as Donovan bodies. Cultivation is difficult.

The diagnosis of LGV is usually based on clinical criteria. Diagnosis on the basis of a genital ulcer or lesion alone is rare. Later, after the onset of tender unilateral inguinal or femoral adenopathy, the diagnosis is most obvious. Isolation by cell culture or identification by NAATs of *C. trachomatis* from bubo drainage is diagnostic. At the present time, commercially available NAATs for chlamydia can identify the organism in rectal specimens but are not approved by the US Food and Drug Administration for this purpose. Further testing with LGV serovar-specific NAATs can be performed, but these NAATs are not widely available. Testing of serum for *C. trachomatis* antibody can be done with the use of complement fixation or microimmunofluorescence techniques but are generally not used.

The lesions of HPV also are diagnosed primarily by their clinical appearance. Resort to biopsy of lesions on keratinized tissue is infrequent. There is no cell culture system for the cultivation of HPV. The presence of virus in nonkeratinized tissue such as cervical epithelium can be assessed by cytologic methods (e.g., Papanicolaou smear) or biopsy. The cytologic change consistent with HPV is the koilocyte, with or without nuclear atypia. Cytology alone can be both insensitive and nonspecific. HPV DNA tests such as hybrid capture or polymerase chain reaction (PCR) used in conjunction with cytologic examination are accurate. Application of 3% to 5% acetic acid to suspicious mucosal lesions reveals the characteristic whitening of HPV lesions on either female or male genitalia. Serologic tests for HPV, useful in epidemiologic and vaccine studies, as of yet have no obvious role in clinical care. Their utility in aiding the diagnosis of a chronic, common problem such as HPV may be an issue.

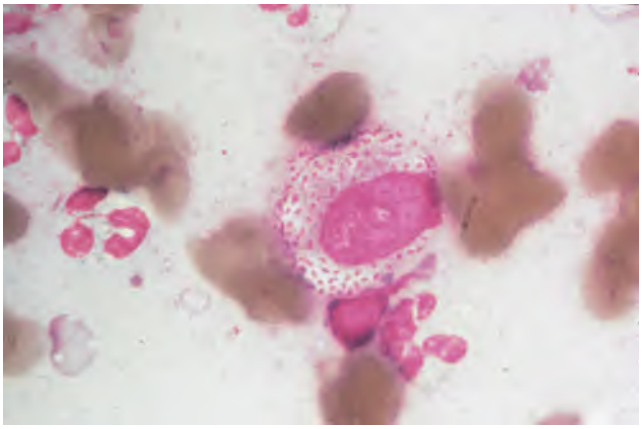

FIG. 106.13 Klebsiella granulomatis. Biopsy of granuloma inguinale lesion showing Donovan bodies consistent with *K. granulomatis.*

Infestation with ectoparasites such as *Sarcoptes scabiei* is demonstrated by identification of the organism, eggs, or feces under direct light microscopy. This may require the unroofing of the scabies burrow bluntly with a needle or scalpel.

NAATs are an increasingly common means of diagnosing infectious diseases including *C. trachomatis* and *N. gonorrhoeae* urethritis. Efforts have been made to apply these technologies to the diagnosis of some of the more common genital lesions. Nucleic acid detection can be performed with the use of hybridization techniques, amplification techniques (i.e., PCR, transcription-mediated amplification, or some combination of both). NAATs have been developed for *H. ducreyi,*[125] *T. pallidum,*[126] and HSV.[122] These technologies have also been combined in one "multiplex" platform (M-PCR) to aid in the clinical evaluation of genital lesions.[127–133,134] The role of such tests in current clinical practice is undefined.

Routine evaluation of genital ulcer disease in the United States should at the very least include viral culture or NAATs for HSV-2 and serologic tests for syphilis. If darkfield microscopy is readily available, it should be used to identify spirochetes. Most laboratories do not have ready access to media for the cultivation of *H. ducreyi.* PCR for *H. ducreyi,* used in some research settings, is highly sensitive and specific but is not approved by the US Food and Drug Administration or widely available.

THERAPY

The goals of therapy include the elimination of the pathogen, resolution of lesions and symptoms, reduction in the risk of transmission, and, if applicable, a reduction in the frequency of recurrences.

After more than 70 years of use, penicillin remains the treatment of choice for the chancre of primary syphilis and the lesions associated with secondary disease. A single intramuscular injection of 2.4 million U of benzathine penicillin G should result in prompt conversion to darkfield-negative lesions and the onset of healing within 24 to 48 hours. Alternatives to penicillin include a course of doxycycline (100 mg orally twice daily for 14 days) or ceftriaxone (1–2 mg intramuscularly or intravenously for 10–14 days).[8] There are far fewer data and little clinical experience supporting the use of these alternative regimens.[135,136] Regardless of the therapy selected, patients treated for early-stage syphilis require serially repeated serologic tests (nontreponemal) even after lesions heal to verify an adequate response. These can be done at 6-month intervals.[21] Fourfold or two-step dilutional decreases indicate an appropriate response. There is no evidence that HIV-infected patients require additional or different therapies for early syphilis.[104] Serologic tests in these patients should be performed at intervals of 6 months or less.

HSV infections can be treated with a variety of related nucleoside analogues available both orally and intravenously. The goal of therapy may be to hasten the resolution of lesions and reduce infectivity or to suppress outbreaks in individuals who experience frequent bouts of disease. Antiviral agents inhibit DNA polymerase and require phosphorylation by viral thymidine kinase to do so. The most commonly used agent, acyclovir, was the first to be marketed. Subsequently, both valacyclovir, a prodrug of acyclovir, and famciclovir, a prodrug of another nucleoside analogue, penciclovir, were introduced for the treatment of HSV. These agents are more bioavailable than acyclovir in oral form and can be dosed less frequently. If necessary, severe HSV genital disease can be treated with intravenous acyclovir. Patients can use these agents for quick resolution of acute outbreaks, for prevention of development of lesions, or for long-term suppression of outbreaks.[137] Regular use of valacyclovir by infected patients has been shown to prevent transmission

to previously uninfected sexual partners.[138] Thymidine kinase–deficient strains of virus, although rare, are resistant to these antivirals. This phenomenon has been observed primarily, although not exclusively, in immunocompromised hosts.[102,115,139–142] Disease caused by resistant isolates can be treated with foscarnet, a DNA polymerase inhibitor unrelated to acyclovir and its congeners.[143] Foscarnet is available only for intravenous use and has been compounded for topical use. It potentially causes renal dysfunction and hypophosphatemia. Another agent that has activity against HSV is cidofovir, an acyclic nucleoside phosphonate.[144] It is also available intravenously and can be formulated for topical use. Pritelivir, a new helicase-primase inhibitor that is unaffected by thymidine kinase deficiency and is available in oral form, is currently under study (see Chapter 46).[145]

Chancroid may be cured microbiologically with a number of antimicrobial agents. Lesions are often slow to heal, and scarring may occur. Although sulfonamides and aminopenicillins were originally used in the treatment of chancroid, microbial resistance has rendered them ineffective. Erythromycin and azithromycin are currently recommended therapies. The latter can be used as a single 1-g dose orally.[8] The third-generation cephalosporin ceftriaxone, given as a single dose of 250 mg intramuscularly, also is effective, but there are concerns about diminished activity in patients with HIV coinfection.[44,146] Fluoroquinolones effectively treat chancroid but should be administered for at least 3 days and not as single-dose therapy.[147] Tender, fluctuant buboes can be aspirated for symptomatic relief.

Although symptomatic HPV infection and molluscum contagiosum may both spontaneously resolve, there is a role for treatment. Therapies include a variety of ablative techniques such as curettage, electrocautery, cryosurgery, and laser. Each of these therapies causes some tissue damage. None provides a certain cure, and recurrence is common. Topical agents include podophyllin (from the resin of the mayapple), trichloroacetic acid, and imiquimod (an immune modulator). Podophyllin should not be used on nonkeratinized epithelium or during pregnancy. Podophyllin and imiquimod also are available for use as patient-applied preparations. Topical application by patients of catechins, a green tea extract, is available and appears to be effective to some degree.[148] Intralesional interferon injections have been studied but are associated with poor response and significant side effects.[149]

Tetracycline congeners and erythromycin have long been the standard therapy for LGV. The duration of therapy is ordinarily 14 to 21 days. There are no data comparing any particular preparation or satisfactorily defining duration of therapy. Reports of successful azithromycin use for LGV have been published, but clinical trials data are lacking.[150] Donovanosis can be treated with a variety of antibiotics including doxycycline, trimethoprim-sulfamethoxazole, fluoroquinolones, and erythromycin. The course of therapy for donovanosis should be 3 weeks or until lesions are healed. Relapse may occur.

OTHER MANAGEMENT ISSUES

Because genital ulcer disease, in particular, and sexually transmitted diseases, in general, seem so closely linked to HIV transmission, it is prudent to make HIV counseling and testing services available to all patients who present with venereal genital lesions. It is also necessary for patients with genital lesions to be counseled about the communicable nature of their disease and the need in many of these instances for partner referral. Based on local public health requirements, it may be necessary to report certain infections to the health department. Sexual partners of patients with syphilis and chancroid require evaluation and therapy for those conditions. In cases of LGV and donovanosis, treatment of asymptomatic partners is of unclear benefit. Partners of individuals with HSV or HPV need counseling about exposure and the potential for disease. The utility of routine cervical Papanicolaou smears for women should be explained. Finally, methods to avoid future infections (e.g., safe sex) should be explored with the patient.

Male circumcision has been garnering attention as a potential way to reduce risk of HIV acquisition. Evidence that this strategy may also reduce risk of genital ulcer disease and other sexually transmitted diseases is conflicting.[131,151,152,153] Condom use remains an important, although not an absolute, measure to prevent infection from the common causes of diseases associated with genital lesions.

NONVENEREAL GENITAL LESIONS

Candida spp., other yeasts, and some molds sometimes cause nonvenereal genital lesions. In women, vaginal colonization with yeast is extremely common, although symptomatic disease occurs in only a fraction of colonized individuals. In a small number of patients, symptomatic disease may be recurrent. Recent use of antimicrobials is a common predisposing risk factor for candidal infections. Vulvovaginal infection is commonly characterized by a thick, whitish, pruritic vaginal discharge, but occasionally it manifests solely as vulvar and perineal disease, with inflammatory vulvitis, erythema, pruritus, superficial excoriations, and ulcerations. Distinguishing candidal lesions on the external genitalia from lesions of other common superficial ulcerative processes such as HSV lesions may at times be difficult.

Genital infection with yeast also occurs in men, a condition known as *candidal balanitis* or *balanoposthitis*. A history of a sexual partner with vulvovaginal infection may be elicited, although sexual transmission is not typical. Balanitis usually involves only the glans, which can appear taut and glossy. There may be multiple, discrete, small pustules and linear or more substantial erosions. As in women, there is often significant pruritus.[35] A proportion of individuals with candidal balanitis have diabetes mellitus.[34] Skin scrapings or vaginal fluid examined under light microscopy after the addition of potassium hydroxide reveal the pseudohyphae of *Candida* spp. Treatment with any of a variety of topical or oral azole antifungal agents is usually effective. Similar findings may be observed with Zoon balanitis, which commonly manifests as an erythematous macule on the penis in uncircumcised men. Plasmocytes predominate on histopathology. These lesions are benign, and topical azoles are generally effective.

Dermatophytes such as *Trichophyton* spp. can cause scaling and sharply demarcated lesions known as tinea corporis or tinea cruris around the genital and the anal area (Fig. 106.14). They can be asymptomatic or mildly pruritic. Infection is usually due to spread from another part of the body.

Fixed-drug eruptions, which represent systemic responses to medication, may involve the genitalia in either sex. A wide range of agents have been implicated including antibiotics such as the tetracyclines and the sulfonamides nonsteroidal antiinflammatory drugs, barbiturates,

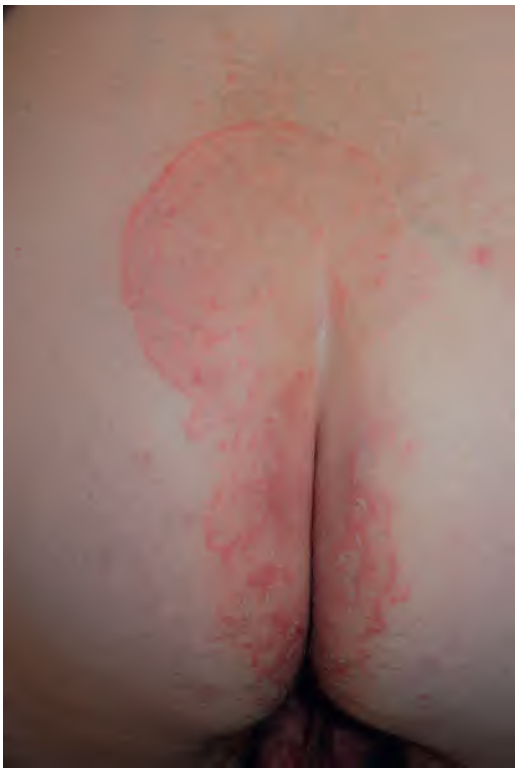

FIG. 106.14 **Tinea corporis.**

and oral contraceptives.[30,31] Lesions occur soon after ingestion of the offending agent, with the development of erythematous or violaceous, sharply demarcated macules. They may recede with residual hyperpigmentation or evolve to form bullae and erosions. Topical medications applied to the genitals can also cause localized contact dermatitis. Other common dermatologic conditions can involve the genitals including eczema and psoriasis.[132] In eczema, pruritus leads to scratching, which then results in linear erosions. When chronic, this can cause lichenification or thickening of the skin. In psoriasis, there is epidermal hyperplasia. Lesions are red, well demarcated, and often scaling. Patients with psoriasis and who have been exposed to therapy with ultraviolet light may be at a higher risk for squamous cell carcinoma of the genitals.[133]

Aphthous ulcers of the vagina occur in Behçet syndrome and in HIV infection.[134,154] The cause of these lesions is unclear, but they are presumably the result of an immune-mediated phenomenon. These lesions are typically small, approximately 1 to 2 mm, but may be quite large in some instances. They may be superficial or deep and often are marked by surrounding erythema. The diagnosis is made by observation, a history of recurrence, and the exclusion of other causes. As with other cutaneous manifestations of Behçet syndrome, they are treated with topical or systemic steroids, colchicine, dapsone, or thalidomide. Lichen planus, another process of presumed immunologic origin, may also cause isolated genital lesions or genital lesions in association with oral lesions.[155] Lichen sclerosus is another possibly autoimmune condition that involves the external genitalia in women. Persistent low-grade inflammation eventually leads to the characteristic fibrosis of the vulva and adjoining structures with occasional extension to the perirectal tissue giving the characteristic white keyhole appearance.

Genital lesions may also arise from other processes including trauma[21,156,157] and folliculitis. Pearly penile papules are anatomic variants characterized by tightly clustered, small, uniform papules exclusively involving the coronal sulcus in a circumferential distribution. They are not rare, often appear in young adulthood, and lead anxious patients to seek clinical care, but they require no intervention. Tuberculosis can cause anogenital fistulas from adjacent, infected genital or gastrointestinal structures or, rarely, primary lesions of the genitals.[141,158,159] Genital lesions rarely result from systemic infection with other pathogens such as *Histoplasma capsulatum* and *Entamoeba histolytica*.[142,160–162] Vulvar and penile squamous cell carcinoma are rare but well-recognized clinical entities usually resulting from HPV infection.[163,164] Erythroplasia of Queryat and Bowen disease are variants of squamous cell carcinoma that occur in men.[165]

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107 Urethritis

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SHORT VIEW SUMMARY

Definition
- Urethritis is an inflammatory condition involving the urethra that is usually caused by sexually transmitted infectious pathogens.

Epidemiology
- Urethritis occurs worldwide.

Microbiology
- Common etiologic agents include *Chlamydia trachomatis, Neisseria gonorrhoeae, Trichomonas vaginalis,* and *Mycoplasma genitalium.*

Diagnosis
- Light microscopy of urethral discharge can be helpful. The presence of polymorphonuclear leukocytes is highly suggestive of inflammation. Gram stain that reveals intracellular gram-negative diplococci suggests *N. gonorrhoeae* (or occasionally *Neisseria meningitidis*). Both can also be cultured using standard agar-based techniques. Nucleic acid amplification techniques are preferred for diagnosis of the other etiologic agents of this condition (see Table 107.1).

Therapy
- Treatment is directed toward the known or suspected pathogen. Infection with *N. gonorrhoeae* is generally treated with third-generation cephalosporins along with azithromycin, but resistance is an emerging concern. Infection with *C. trachomatis* responds to azalides and tetracyclines.

Prevention
- Condom use or abstaining from high-risk sexual activity reduces the risk for urethritis.

The symptoms of urethritis range from the trivial and often overlooked to the disabling.[1] Urethral discharge in men may be apparent at all times during the day and may be present in sufficient quantity to stain undergarments or may be scant. It may be clear, mucopurulent, or frankly purulent, and it may be white, yellow, green, or brown. Some patients report only a deviation of the first morning urine stream, whereas others report only a urethral discomfort. Occasionally, urethral discharge comes to the attention of the patient through the observation of mucus strands in the urine.

The urine stream transiently eliminates most inflammatory discharges; therefore discharge is best observed before urination. Micturition immediately preceding urethral examination may completely eliminate signs of infection.

Dysuria is common with urethritis, and men variously localize it to the meatus, the distal portion of the penis, or anywhere along the shaft. Dysuria is sometimes increased by the acidity or solute content of the urine and therefore may be most marked during the passage of concentrated first morning urine. It may be increased in the presence of irritants such as alcohol, which is an observation that sometimes leads the patient to attribute his disease to the ingestion of specific foods or fluids. Discomfort may persist between micturitions and is perceived as pain, itching, frequency, urgency, or a feeling of heaviness in the genitalia.

Discomfort experienced only during ejaculation, deep pelvic pain, or pain radiating to the back is infrequent in uncomplicated urethritis and suggests prostatitis or inflammation involving other portions of the urogenital tract such as the epididymis. Hematuria (particularly if painless) and blood in the ejaculate are uncommon in urethritis. The persistence of hematuria after cure of urethritis demands a thorough urologic evaluation.

Exclusive urethral infections are less well described in women. Dysuria is a very common symptom among women and may be due to cystitis, urethritis, or vulvitis. Urethritis is most likely due to a sexually transmitted pathogen and is often associated with concomitant cervicitis. The term *acute urethral syndrome* has been used to describe urethritis in women that is largely due to *Chlamydia trachomatis* infection; this is discussed later (see "Urethral Syndrome and Related Diseases of Women").

The epidemiology of urethritis varies with the geographic prevalence of the causative organisms. The most data are available for gonococcal and chlamydial infections. Surveillance data from the Centers for Disease Control and Prevention (CDC) reveal increases in case rates for gonococcal and chlamydial infections in both men and women throughout the United States.[2] Rates are disproportionately high for minority populations in the United States, especially among non-Hispanic blacks.[2] The highest rates are seen among men and women 20 to 24 years of age. It is unknown whether rate increases relate to enhanced screening programs, including modifications in testing procedures with addition of extragenital testing, or true increase in disease transmission.[2] Worldwide data vary considerably by locale. Gonococcal and chlamydial rates vary across Europe, although reported rates in men, especially men who have sex with men (MSM), have increased in recent years.[3]

EXAMINATION OF THE URETHRA

The male genitalia are best examined while the patient is supine. Alternatively the man can stand before the seated examiner so that the external genitalia are at approximately eye level. The entire genital area should be visualized. The underwear may reveal stains of dried discharge, suggesting that it is being produced in large amounts.

The patient is preferably examined at least 2 hours after his last micturition. If advised to restrict fluids during the day preceding the examination, the patient may be able to present for evaluation before passing the first urine of the day, which sometimes permits the recovery of very small amounts of discharge.

The entire genital area should be carefully examined because acquisition of more than one sexually transmitted infection is relatively common. Inguinal adenopathy should be palpated to evaluate for tenderness and enlargement. If lymphadenopathy is present, bilateral versus unilateral findings should be noted. The skin of the entire pubic area, scrotum, groin, and penis should be examined for lesions, and the hair should be examined for nits. The testes, epididymis, and spermatic cords should be palpated for masses or tenderness. The foreskin should be completely retracted and the glans examined. The urethral meatus should be inspected for crusting, redness, and spontaneous discharge. If no discharge is present, the urethra should be gently stripped as follows. The examiner places the gloved thumb along the ventral surface of the base

of the penis and the forefinger on the dorsum and then applies gentle pressure; the hand is moved slowly toward the meatus. This maneuver frequently expels a discharge that may be collected on a swab for examination (as described later).

If no discharge is delivered by this maneuver, the third and fourth fingers should be used to grip the penis lightly from above, just behind the glans. The thumb and forefinger can then spread open the meatus to examine for urethral redness or the presence of small amounts of discharge. Unless the patient has recently urinated or has been in a state of sexual arousal, virtually no fluid should be expressible from the urethra or observed by spreading the meatus.

If expressed material cannot be collected at the meatus, a specimen must be obtained from inside the urethra. This is best accomplished with a small urethral swab. The swab should be inserted gently at least 2 cm into the urethra, with care taken not to attempt to force the tip past any obstruction. The patient should be warned that the procedure will be uncomfortable; also, the insertion and removal of the swab should be accomplished as quickly as possible. Patients tolerate the procedure better in the supine position. If additional specimens are required for multiple examinations or cultures, separate swabs should be used, and each one should be inserted at least 1 cm deeper than the one preceding it.

Regular cotton swabs should not be used for urethral examination because their larger diameter makes insertion extremely uncomfortable and because of the possibility that the cotton or the wooden shaft may be toxic to some fastidious pathogens. Currently available nucleic acid amplification test (NAAT) kits provide swabs appropriate in size and composition to obtain a proper specimen.

The female urethra is best examined when the patient is in the lithotomy position. The entire genital area should be examined for lesions and discharge, and the vagina should be examined as described in Chapter 108. The urethral meatus may be directly visualized, and the urethra may be stripped by placing the gloved finger inside the vagina and gently moving it along the urethra. A urine specimen may be examined by light microscopy, culture, or NAATs for the presence of typical pathogens.

EXAMINATION OF THE URETHRAL SPECIMEN AND CONSIDERATION OF ETIOLOGIES

A swab that contains material from the urethra should be rolled across a clean microscope slide. Rolling rather than streaking the swab brings all its surfaces into contact with the slide and better preserves cellular morphology. The material should be air dried and fixed by gentle heating or by rinsing with methanol. Gram staining of urethral material is particularly useful in the workup of urethritis (Table 107.1), and the specimen should be examined with the use of the oil-immersion objective. Specimens obtained from within the urethra usually contain urethral epithelial cells. If recovered from near the meatus, these are typical squamous cells with a very large cytoplasmic-to-nuclear ratio; if obtained from further within the urethra, they are cuboidal epithelial cells, which are smaller and have relatively larger, less dense nuclei.

TABLE 107.1 Evaluation of Men Who Have Urethral Symptoms

DIAGNOSTIC STUDIES	COMMENTS
Gram-stained urethral smear	
Examination of first-void urine specimen for leukocytes	
Endourethral cultures or nonculture tests	
Neisseria gonorrhoeae	Culture and NAAT equally appropriate; culture can provide option for susceptibility testing
Chlamydia trachomatis	NAAT preferred
Trichomonas vaginalis	Culture or NAAT
Mycoplasma genitalium	No currently available commercial test

NAAT, Nucleic acid amplification test.

Urethral material from patients with acute urethritis contains polymorphonuclear neutrophils (PMNs) (Table 107.2). The area of the smear that contains the most PMNs should be sought. More than two PMNs per oil-immersion microscopic field is abnormal and is seen in most patients with acute symptomatic urethritis.[4] However, although the positive predictive value of urethral PMNs is quite good, the negative predictive value for infection is not. As many as 15% of men with documented urethral infection do not show significant numbers of PMNs in Gram-stained smears.[4,5] The number of PMNs in the smear is reduced by recent micturition; also, often there is considerable observer variation in the number of PMNs detected in a single specimen.[6] Therefore although purulent discharges may reveal sheets of PMNs, the minimal number of these cells that indicates disease is not known. In general the presence of even rare PMNs suggests infection, particularly in a patient who has urethral symptoms, who engages in high-risk sexual activity, or who is found to have a small amount of discharge on examination.

The distal centimeter of the urethra is colonized by normal skin or introital microbiota. The smear usually contains a variety of gram-positive and gram-negative organisms that have no particular significance. Of great diagnostic value, however, is the presence of typical gram-negative, "intracellular" diplococci (Fig. 107.1). These organisms are not randomly distributed among the cells but are seen in large numbers in a few PMNs. They are observed in more than 95% of all symptomatic patients with gonococcal urethritis and in less than 2% of all symptomatic men who cannot be shown to have gonorrhea by culture.[7] Some strains of *Neisseria gonorrhoeae* are inhibited by the concentrations of vancomycin that usually are employed in selective isolation media (i.e., Thayer-Martin, Martin-Lewis); these organisms will not be recovered by standard culture techniques.[8] Extracellular diplococci indicate gonorrhea in only 10% to 29% of all cases, and this predictive value is reduced even further in populations with a low prevalence of gonorrhea. A shortcoming of the Gram-stained smear is that coincidental infection with the agents responsible for most cases of nongonococcal urethritis (NGU) cannot be diagnosed in the presence of gonorrhea. Although a smear containing PMNs that does not reveal gram-negative intracellular diplococci suggests NGU, a smear revealing these organisms does not rule out concomitant infection with *C. trachomatis, Mycoplasma genitalium,* or *Trichomonas vaginalis.* Trichomonads are nearly impossible to identify on Gram-stained smears. Urethral material may be mixed with a small amount of saline and observed as a wet mount with the

TABLE 107.2 Objective Evidence of Urethritis

Visibly abnormal discharge (purulent, mucopurulent)
Urethral Gram stain containing ≥2 leukocytes per oil-immersion field
First-void urine specimen containing >10–15 leukocytes per high dry field

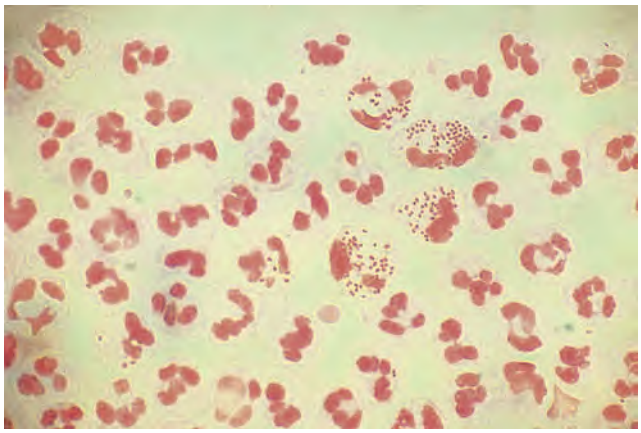

FIG. 107.1 Gram stain of urethral exudate from a man with gonorrhea. Several neutrophils contain many gram-negative cell-associated diplococci.

substage condenser racked down or the substage diaphragm partially closed. Motile trichomonads occasionally are observed but are rarely seen unless the urethral material for examination is obtained before the first voiding. Positive findings on a wet mount are diagnostic of trichomoniasis, but findings on the wet mount are often negative in infected men. Endourethral cultures and cultures of first-void urine sediment in liquid media such as modified Diamond medium are useful in the diagnosis of trichomoniasis in men.[9,10] NAATs for *T. vaginalis* infections are now available.[11] *Mycoplasma* does not have a cell wall and lacks the macromolecules in its membrane to be well-visualized by Gram stain.

After the man's urethra has been carefully examined, he may be asked to provide a divided urine specimen. The patient delivers the first 10 mL of urine into one container and a midstream urine specimen into a second container. The presence of mucus strands in the first fraction that clears in the second portion suggests urethritis. Equal aliquots of the fractions may be centrifuged and the sediments examined as wet mounts. Observation of more white blood cells in the initial fraction than in the second fraction suggests urethritis, whereas equal numbers of white blood cells in both fractions suggests cystitis or infection higher in the urinary tract. The presence of more than 10 to 15 white blood cells in 400× microscopic fields of the sediment from the initial fraction strongly suggests urethritis, but the minimum significant number of white blood cells is unknown.

The presence of white blood cells in the initial urine fraction provides no clue to the cause of urethritis. Such a finding, however, may allow an objective diagnosis of urethritis to be made in a man whose Gram-stained smear does not contain PMNs.

Some men who are infected with *N. gonorrhoeae* and many men infected with *C. trachomatis* have no symptoms. Such men often have pyuria that can be detected by examination of the first 10-mL urine sample by either microscopy[12] or leukocyte-esterase dipstick testing.[13] This approach provides a noninvasive, inexpensive method for screening men for urethral infection. Men found to have pyuria are candidates for further examination, including examination of endourethral specimens for gonococci, chlamydiae, and trichomonads.

If the urine specimen is a first morning micturition, motile trichomonads may be observed in the sediment. In one study, *T. vaginalis* organisms were recovered by culture of urethral swabs in 80% and first-void urine in 68% of infected patients. When combined, these two cultures were detected in 49 (98%) of 50 infected men.[9] As in the case of endourethral specimens, NAATs of urine are the most sensitive and specific means of identifying *T. vaginalis*.[14]

NAATs have replaced culture as the test of choice for identification of *C. trachomatis* organisms.[15] Material recovered from the urethra can be cultured on appropriate media for *N. gonorrhoeae*. Nonculture tests (i.e., NAATs) are also available for detection of *N. gonorrhoeae* organisms. These tests are considered the test of choice for diagnosis of mucosal gonococcal infections unless antibiotic susceptibility information is needed.[15] Importantly, most nonculture tests for chlamydiae are "bundled" with a nonculture test for gonococci, and some include testing for *T. vaginalis* as well.[15]

Neisseria meningitidis has been increasingly recognized as a pathogen associated with urethritis. Recent outbreaks in Ohio, Michigan, and Indiana have been in predominantly heterosexual men, and sequencing has revealed *N. meningitidis* ST11.[16,17]

Suspicion should be raised when a urethral Gram stain indicates gram-negative intracellular diplococci and a corresponding urine or urethral nonculture test is negative for the presence of *N. gonorrhoeae*. *N. meningitidis* can grow in appropriate culture media (i.e., Thayer-Martin, Martin-Lewis). *N. meningitidis* urethritis was confirmed in an outbreak investigation by culture and biochemical identification and polymerase chain reaction (PCR) testing.[16,17]

Other pathogens may also warrant consideration during urethral examination. *M. genitalium* is estimated to cause 15% to 20% of NGU cases and 30% of persistent or recurrent urethritis.[18,19] PCR assays are the most sensitive tests for this fastidious organism.[20] *Ureaplasma urealyticum* has been subdivided into two species—*Ureaplasma parvum,* which is a saprophyte, and *U. urealyticum,* which may be a cause of urethritis (see later discussion). NAATs for *U. urealyticum* are also available. Although they are present in the distal urethra, normal skin organisms (e.g., *Staphylococcus epidermidis,* α-hemolytic streptococci, propionibacteria) and vaginal organisms (e.g., *Candida albicans,* lactobacilli, *Escherichia coli, Gardnerella vaginalis*) are of no diagnostic significance.

NONINFECTIOUS URETHRITIS

The genital tract is psychologically important, and trivial symptoms are often worrisome to patients. The "worried well" make up a significant fraction of men who are seen in sexually transmitted infection clinics and in private practices. Detailed questioning as to why the patient perceives he has a genital infection may reveal guilt over masturbation or an extradyadic (e.g., extramarital) sexual contact. The urethral specimen in these cases usually reveals normal epithelial cells and no white blood cells. Some patients confuse dried remnants of semen with inflammatory discharge. Spermatozoa may be recognized on the Gram stain as gram-positive ovoids whose coloration fades gradually toward the acrosomal cap. Spermatozoa may also be recognized on the wet mount. However, the clinician must remember that symptoms and signs of true urethritis can be trivial and that microscopic examination may miss minimal inflammation, particularly if the patient has recently voided. Symptomatic patients with negative examination results should have urethral or urine specimens tested for urethral pathogens and be asked to return in several days, by which time the symptoms may have resolved or examination may provide a diagnosis. Antimicrobial treatment of symptomatic men who have neither objective evidence of urethritis nor positive cultures for urethral pathogens is inadvisable and may serve to reinforce psychosomatic contributions to their symptoms.[21] Occasionally, a patient who reports discharge actually has urinary incontinence.

Chronic irritation of the urethra can elicit a clear, mucoid discharge. Occasionally, patients who are concerned that they may have contracted a venereal disease vigorously strip the urethra looking for discharge. After several days of this trauma, a clear discharge obligingly appears that may contain a few white blood cells. A history of vigorous urethral stripping is helpful diagnostically. Patients who are receiving treatment for other forms of urethritis should be cautioned not to examine themselves too vigorously for fear that such a traumatic discharge may confuse the clinical picture. Very rarely, patients insert foreign bodies into the urethra and produce a mechanical urethritis.[22]

A heavy precipitation of crystals in the urine can suggest a discharge, and the presence of large amounts of crystalline material or calculous gravel can produce urinary discomfort. The intermittent nature of pain associated with the passage of gravel or the obvious presence of crystals on microscopic examination of the urine sediment usually confirms this diagnosis. White blood cells may be present.

Chemicals can irritate the urethra, and alcohol has long been known to produce mild dysuria. The ingestion of alcohol during treatment for gonorrhea was at one time thought to be responsible for the syndrome of postgonococcal urethritis (discussed later), although postgonococcal urethritis is now known to have an infectious etiology. Occasionally a patient develops urethral symptoms on contact with vaginal chemicals such as spermicides used by a sexual partner. The history of discomfort immediately after sexual contact may be suggestive. This condition should be diagnosed only after other possible causes have been excluded.

INFECTIOUS URETHRITIS

Gonococcal and Nongonococcal Urethritis

The classic specific etiologic agent of acute urethritis is *N. gonorrhoeae*. Urethral infection of all other causes is referred to collectively as NGU (Table 107.3). As with gonorrhea, NGU is a sexually acquired condition. NGU is more common than gonorrhea in the United States and in much of the developed world. In some developing areas, however, gonorrhea accounts for up to 80% of cases of acute urethritis.[23–25] Similar to many other sexually transmitted diseases (STDs), gonococcal urethritis and NGU have an increased incidence during the summer months, presumably because of a seasonal increase in sexual activity.

FIG. 107.2 Purulent urethral discharge from a man with gonococcal urethritis.

FIG. 107.3 Mucopurulent urethral discharge from a man with nongonococcal urethritis.

TABLE 107.3 Most Common Infectious Causes of Urethritis

Neisseria gonorrhoeae
Chlamydia trachomatis
Trichomonas vaginalis
Mycoplasma genitalium
Herpes simplex virus
Adenovirus
Ureaplasma urealyticum
Neisseria meningitidis

Compared with gonococci, the organisms that cause NGU may be relatively less prevalent among MSM than among heterosexual men with urethritis. In a study of men who had urethritis, Ciemins and colleagues[26] recovered gonococci from 45% of MSM and from 26% of men who have sex with women. Examining consecutive men attending an STD clinic, Stamm and colleagues[27] recovered gonococci from 12% of heterosexual men and 25% of MSM; in contrast, chlamydiae were recovered from 14% of heterosexual men but only 5% of MSM. Other studies demonstrate similar findings.[28–30] Studies have associated fellatio with the acquisition of gonococcal urethritis and NGU in MSM but not in heterosexual men.[31,32]

Urethritis may facilitate transmission of human immunodeficiency virus (HIV). Among patients infected with HIV, the quantity of HIV in urethral secretions is increased if the man has concomitant chlamydial or gonococcal urethritis. Treatment of urethritis reduces the urethral viral load.[33]

The clinical spectrum of gonorrhea differs from that of NGU, but there is sufficient overlap that an accurate diagnosis must be based on examination of the urethral specimen. Of men who acquire urethral gonorrhea, 75% develop symptoms within 4 days, and 80% to 90% do so within 2 weeks.[34] The incubation period for NGU is much more variable and is often longer. Incubation periods ranging from 2 to 35 days have been described, but almost 50% of men with NGU developed urethral symptoms within 4 days.[34] Therefore an incubation period of less than 1 week is not a reliable factor in the differential diagnosis. The incubation period of either infection can be prolonged by the ingestion of subcurative doses of antibiotics.

The urethral discharge is described as frankly purulent in three-fourths of patients with gonorrhea (Fig. 107.2) but in only 11% to 33% of patients with NGU.[7,35] A purulent discharge issuing from the meatus without stripping of the urethra correlates strongly with the diagnosis of gonorrhea but is also seen in 4% of patients with NGU.[7,35] Mucopurulent discharge (Fig. 107.3), consisting of thin, cloudy fluid or mucoid fluid with purulent flecks, is seen in about 50% of patients with NGU but in only 25% of patients with symptomatic gonorrhea.[7,35] The discharge is completely clear and moderately viscid in 10% to 50% of patients with NGU, principally patients who are minimally symptomatic, but in only 4% of symptomatic patients with gonorrhea.[7,35,36] A diagnosis based on the clinical characteristics of the urethral discharge is unreliable and correctly identifies the causative disorder in only 73% of all cases, even under optimal circumstances.[35] Microscopic examination always should be part of the initial evaluation.

Dysuria has been described in 53% to 75% of patients with NGU and in 73% to 88% of patients with symptomatic gonorrhea.[7] Only about 10% of patients reporting dysuria without discharge have gonorrhea; the remainder have NGU.[7] A combination of dysuria and discharge is seen in 71% of patients with gonococcal urethritis but in only 38% of patients with NGU. Therefore the combination of discharge and dysuria is associated with gonorrhea, whereas the appearance of one without the other is more frequently seen with NGU. However, the association is not sufficiently specific for differentiating these two entities. Urethral discomfort can mimic cystitis in men and women and can result in urinary frequency and urgency.

Symptoms of gonorrhea often begin abruptly, and the patient may remember the specific time of day when they were first noted. NGU usually has a less acute onset, with symptoms increasing over several days. A urethral discharge may appear days in advance of dysuria; the symptoms may wax and wane, even to the point of transiently disappearing before the patient seeks therapy. The mildness and variability of the symptoms may erroneously convince a patient with NGU that he does not have a significant disease; such patients often delay seeking medical attention.[7]

In most cases, the symptoms of infectious urethritis resolve even if the causative disorder remains untreated. Of patients with acute gonococcal urethritis, 95% who do not receive treatment are free of symptoms 6 months after contracting the disease,[37] and the symptoms of NGU gradually subside over a period of 1 to 3 months in 30% to 70% of patients.[38] How many of these asymptomatic patients remain infected and potentially infectious is unknown. Untreated gonococcal urethritis may subside to a chronic state characterized by little or no urethral discomfort and a small amount of mucoid discharge called *gleet*. This discharge contains small numbers of gonococci and PMNs.

Because of the great clinical overlap between NGU and gonococcal urethritis, a diagnosis should not be made on clinical grounds alone. Gram staining of urethral discharge material reveals typical gram-negative, intracellular diplococci in about 95% of patients with symptomatic gonococcal urethritis and is negative in about 97% of patients with symptomatic NGU.[7] Therefore in a population in which about 50% of the cases of acute urethritis are gonococcal, a positive result on Gram staining suggests gonorrhea and a negative result suggests NGU with 98% accuracy.[7] Typically shaped extracellular diplococci are found in about 15% of patients with symptomatic urethritis.[7]

The sensitivity of the culture for *N. gonorrhoeae* is less than 100%. The chances of isolating the organism are further reduced if the patient has recently taken antibiotics or if there is a delay in processing the culture. Therefore it is likely that most of the few patients with positive findings on Gram staining and negative cultures actually have gonorrhea.

In most cases of acute symptomatic urethritis, culture is unnecessary to confirm Gram stain findings diagnostic of gonorrhea. It must be remembered that results on Gram staining are negative in as many as 5% of patients who have gonorrhea, so Gram stain findings suggestive of NGU should be confirmed with a culture or nonculture test for gonococci, although therapy need not be delayed until the results are known. Results on Gram staining cannot be used to make a diagnosis of simultaneous NGU in the presence of gonorrhea. Because of the frequency with which trichomonads are missed with direct microscopic techniques, patients in whom trichomonal urethritis is suspected should be evaluated by culture of urethral and first-void urine specimens[10] or, if available, NAAT.

There is no doubt that urethritis is sexually transmitted. It occurs most frequently during the ages of peak sexual activity and in groups with a high prevalence of other STDs. It frequently occurs after sexual exposure to a new partner and is almost never seen in virgins except as a part of some systemic conditions. As the etiologic agents of urethritis have been defined, they have been isolated with high frequency from the female and male sexual partners of infected men, in whom the agents usually are carried asymptomatically.

Recognition of urethritis as an STD is important for several practical reasons. It allows definition of a population at very high risk for carrying the causative agents, namely, the sexual partners of infected patients. The prevalence of infection with these agents is sufficiently high among sexual partners to justify their treatment on epidemiologic grounds even if they are asymptomatic. Many episodes of recurrent urethritis are terminated only by the treatment of an asymptomatic sexual partner of the infected patient. Because patients with one STD are at increased risk for others, it is important to screen patients with urethritis for other STDs.

Etiology of Nongonococcal Urethritis

The organism most clearly associated with NGU, *C. trachomatis,* is discussed in detail in Chapter 180. However, this obligate intracellular parasite causes only 20% to 50% of cases of NGU.[39–41] Effective *Chlamydia* control programs have reduced the proportion of men with NGU who are infected with *C. trachomatis. C. trachomatis* is susceptible to several antimicrobial agents, including tetracyclines, sulfonamides, erythromycin, and azithromycin. Significantly, it is not reliably eradicated by cephalosporins. Chlamydiae are not recovered from at least 50% of men with NGU. The clinical features of chlamydia-negative NGU are very similar to the features of chlamydia-positive NGU.[42]

The agents responsible for chlamydia-negative NGU are incompletely identified. *U. urealyticum,* whose role in NGU is controversial, has been reclassified into two species: *U. parvum* (biovar 1) and *U. urealyticum* (biovar 2).[20] *U. parvum* may be a commensal organism, whereas *U. urealyticum* may be one of the true causative agents of chlamydia-negative NGU.[43–45] Accurate assessment of the relative contribution of ureaplasmas has been hindered by the ubiquity of the organisms that can be recovered from urethral cultures from many sexually experienced men who have no evidence of urethritis.[46] *Mycoplasma hominis* is not a cause of NGU,[47] whereas *M. genitalium* has been recovered from patients with NGU and is now a recognized cause of this condition.[48–50] Studies in which this fastidious organism was identified with the use of PCR assays identified *M. genitalium* in men with NGU more often than in symptom-free control subjects.[51–53]

Similar to *C. trachomatis, U. urealyticum* and *M. genitalium* organisms are susceptible to erythromycin, azithromycin, and, usually, tetracyclines—the agents that have been most successful in treating NGU. However, resistance may be increasing. Perhaps 2% to 7% of patients are infected with tetracycline-resistant *U. urealyticum*[54]; such patients may not be cured by tetracycline therapy. *M. genitalium* may fail to respond to therapy with commonly used therapies for NGU.[55,56]

Dysuria is described by 83% of women and 44% of men with primary herpes simplex virus (HSV) genital infection. Some men notice a clear, mucoid discharge that seems disproportionately mild relative to the degree of dysuria that they experience. HSV is recovered from the urethras of about 80% of women and 30% of men with primary infection, and HSV must be regarded as a cause of some cases of NGU. In most such instances, however, the diagnosis of HSV is obvious because of typical genital lesions. Urethral involvement is less common in recurrent disease, and dysuria is described by only 27% of women and 9% of men.[57]

T. vaginalis organisms have been identified with use of NAATs from more than 20% of men attending urban STD clinics in the United States.[58,59] Identification of *T. vaginalis* has been associated with signs and symptoms of urethritis. The syndrome is not clinically distinguishable from NGU of other causes.

Although rare urethral infection with gram-negative bacilli can be seen in men with diabetes and in men who practice insertive anal intercourse, it may occur in patients with phimosis and in patients with urethral trauma after instrumentation or indwelling catheterization.[60] Periurethral abscesses can occur in this setting. Syphilis, with an endourethral chancre, and intraurethral condylomata acuminata occasionally cause a urethral discharge. *N. meningitidis*[61] and *Moraxella catarrhalis*[62] have been isolated from patients with urethritis. One study[63] identified adenovirus more often in patients with than without urethritis. In another study, in 102 heterosexual men and MSM with urethritis, adenovirus urethritis was diagnosed by urine or urethral PCR or urethral testing. Adenovirus was the exclusive pathogen identified in 93% of the cases.[64] The most frequent symptom was dysuria (83% of patients), and the most consistent physical finding was erythema of the penile meatus (83% of patients). Urethral discharge was noted in 59% of patients, and signs of conjunctivitis were noted in 38% of patients.[64]

In summary, *C. trachomatis,* adenovirus, *M. genitalium, T. vaginalis,* and HSV have been convincingly implicated as etiologic agents in NGU. This has not yet been proven for *U. urealyticum* biovar 2.[65] A significant minority of men with NGU are not infected with any of the aforementioned organisms.

POSTGONOCOCCAL URETHRITIS

Some patients with acute gonococcal urethritis who receive a single-dose treatment with one drug experience prompt resolution followed in a few days by a recurrence of symptoms—usually a mucoid or mucopurulent discharge and sometimes mild dysuria. In other patients, the symptoms never entirely disappear and, after initial rapid improvement, stabilize at a low level. This syndrome has been referred to as *postgonococcal urethritis* (PGU)[66,67] and should be suspected in the event of findings of signs, symptoms, or laboratory evidence of urethritis 4 to 7 days after single-drug treatment for gonorrhea. PGU is a manifestation of dual urethral infection. Gonococci and the agents of NGU are extremely prevalent in sexually active populations, and they are carried simultaneously and asymptomatically by many women. Male sexual partners of these women may acquire both agents during the same sexual exposure. In the presence of gonorrhea, coincident NGU cannot be diagnosed with Gram staining. Single-dose treatment of gonorrhea with an appropriate cephalosporin such as ceftriaxone eradicates the gonococci, eliminating the symptoms of gonorrhea, but it usually spares the agents of NGU. Once the incubation period of NGU is exceeded, the patient experiences a recurrence or persistence of milder symptoms that is consistent with the latter infection.

Although PGU was originally thought to result from the consumption of alcohol or other irritants during therapy for gonorrhea, dual infection is now well established as the explanation. *C. trachomatis* has been recovered from 11% to 50% of men with gonorrhea[39]; 75% to 100% of patients with gonorrhea who are also culture positive for chlamydia will develop PGU if the gonorrhea is treated with an agent that does not eradicate chlamydia.[68] *C. trachomatis* can be recovered from almost 50% of patients with PGU, which is similar to the recovery rate in NGU. However, PGU also develops in up to 50% of the patients with gonorrhea from whom chlamydiae are not recovered. Presumably these cases are due to coinfection with gonococci and other agents of NGU such as *M. genitalium, T. vaginalis,* HSV, adenovirus, and perhaps *U. urealyticum.* As might be expected, if gonorrhea is treated with a regimen active against the agents of NGU, the incidence of PGU is lower.[68] Accordingly, current treatment schedules for gonorrhea include a second agent such as azithromycin or doxycycline. Even if not considering coinfection, currently recommended treatment for gonococcal infection includes therapy active against *C. trachomatis,* so PGU attributable to untreated *C. trachomatis* and most *M. genitalium* strains should be relatively rare.

PERSISTENT OR RECURRENT URETHRITIS

Patients with persistence or recurrence of urethral symptoms after therapy for acute gonococcal urethritis may have PGU attributable to agents of NGU, but gonococcal reinfection and frank treatment failure are also possible especially in an era when diminished susceptibility to antimicrobial agents among *N. gonorrhoeae* strains is increasing. The patient who is experiencing recurrent urethritis must be evaluated as a new patient to differentiate gonococcal from nongonococcal infection. Such patients should have objective evidence of urethritis. When taking a history of persistent or recurrent urethritis, it is important to consider reexposure due to untreated or partially treated partners as well as medication compliance. When these factors have been ruled out and the patient has received a repeat NAAT for *N. gonorrhoeae* and *C. trachomatis,* alternative pathogens such as *M. genitalium, T. vaginalis,* HSV, adenovirus, and perhaps *U. urealyticum* should be considered. If available, NAATs for *M. genitalium* and *T. vaginalis* can be performed. Empirical therapy if chosen should cover the most likely pathogens. If suspicion for reexposure is high, a patient should receive the initial regimen again. Alternatively, treatment for *M. genitalium* should be administered, and potentially treatment for *T. vaginalis* should be given for refractory urethritis.[19]

ASYMPTOMATIC URETHRAL INFECTION

Patients without specific symptoms that are referable to the urethra may be found to have signs of urethritis on physical examination. Sexually transmitted pathogens can be recovered from some patients who have neither symptoms nor signs of urethritis.

The importance of asymptomatic urethral gonococcal infection in men is well recognized.[69] Prolonged asymptomatic urethral carriage of gonococci occurs in 2% to 3% of newly infected men; however, because these men do not seek treatment and because asymptomatic urethral infection may persist for months, the prevalence of asymptomatic urethral gonococcal infections among all men harboring *N. gonorrhoeae* may be 50%.[70] This may have considerable epidemiologic significance. Random screening of asymptomatic men is unrewarding[69] except in high-risk populations. Most cases of asymptomatic urethral infection are detected after gonorrhea is diagnosed in sexual partners or if complications subsequently develop in the infected man. Up to 40% of the asymptomatic sexual partners of women with disseminated gonococcal infection or pelvic inflammatory disease are found to be infected. Asymptomatic gonorrhea may be diagnosed by examination of Gram-stained urethral material collected on a swab with a sensitivity of about 70%.[69] Therefore culture or NAAT for gonococci is the most appropriate diagnostic test.

Asymptomatic urethritis in many cases can be rapidly detected by observing PMNs in material recovered from the urethra with a swab or loop. Endourethral sampling, however, is uncomfortable and is poorly accepted by asymptomatic men. Examination of a first-void urine specimen for leukocytes or leukocyte esterase or for evidence of gonococcal or chlamydial infection with an NAAT[71,72] is a more acceptable means of examining men for asymptomatic urethral infection.[64]

Because of the frequency of asymptomatic, sexually transmitted urethral infections in men, asymptomatic sexual partners of infected individuals should always be evaluated. Because immediate diagnostic techniques are of relatively low sensitivity, such men should receive treatment at the time of their initial presentation (i.e., epidemiologic treatment).

URETHRAL SYNDROME AND RELATED DISEASES OF WOMEN

Dysuria, frequency, urgency, and nocturia are common symptoms of bacterial cystitis in women. A similar syndrome, termed *acute urethral syndrome,* occurs in women who do not have classic bacterial infection of the lower urinary tract.[73,74] The usual workup for bacterial urinary tract infection is unrewarding because less than 10^5 uropathogens are recovered from each 1 mL of urine. Some of these patients appear to have bacterial cystitis, although bacteria are recovered from the urine in smaller than usual numbers.[73,74] In other patients, the symptoms appear to be related to urethritis rather than cystitis. *Escherichia coli* sometimes causes urethritis in the absence of cystitis.[75] If ordinary bacterial pathogens associated with urinary tract infections are not isolated (even in small numbers), the condition is often caused by sexually transmitted agents.[73,74] If pyuria is absent, cultures for enteric bacteria and agents of STDs are less likely to be positive, and antimicrobial treatment is less likely to be effective; a noninfectious explanation for urethral symptoms should be sought in such patients.

N. gonorrhoeae can affect the urethra in women as it does in men and may occasionally cause the urethral syndrome.[76] Gentle stripping of the urethra as described in the earlier section "Examination of the Urethra" may deliver a purulent discharge that on Gram staining reveals typical gram-negative, cell-associated diplococci. Culture or NAAT or both will be positive for *N. gonorrhoeae.* In about three-fourths of affected women, gonococci are recovered from the endocervix as well. The syndrome responds to standard therapy for uncomplicated anogenital gonorrhea (see Chapter 212).

C. trachomatis may be recovered from the urethra in women with dysuria, frequency, and pyuria.[73,74] Urinary tract symptoms are described by about half of women in whom *C. trachomatis* is isolated from the urethra.[77] In such patients, if initial drug therapy includes antimicrobial agents that are active against chlamydiae (e.g., tetracyclines, amoxicillin, fluoroquinolones, sulfonamides, azithromycin), clinical improvement with resolution of symptoms is likely.

Dysuria is a common symptom of women with trichomoniasis. The parasite is recovered from the urethra and periurethral glands in more than 90% of women with the infection (see Chapter 280) and is associated with pyuria. Dysuria also may result from vulvar irritation such as that accompanying vaginal candidiasis, in which case the dysuria is often perceived by the patient as being external. Dysuria is unusual in patients with bacterial vaginosis.

Among sexually active women, infection with uropathogens such as gonococci, chlamydiae, and trichomonads should be ruled out before other therapies are tried.

COMPLICATIONS OF URETHRITIS

Both *N. gonorrhoeae* and *C. trachomatis* have been identified as causes of acute epididymitis among sexually active men.[78] Epididymitis could conceivably lead to infertility, although an association between infectious epididymitis and infertility in men has not been convincingly demonstrated.[79] In 20% to 30% of men with NGU, prostatic involvement can be documented; however, it is usually asymptomatic[80] and responds to standard treatments. The role of organisms that cause urethritis in the development of chronic prostatitis–chronic pelvic pain syndrome remains unclear. Krieger and Riley[81] evaluated prostatic biopsy specimens from 135 men with chronic prostatitis–chronic pelvic pain syndrome with use of PCR assays. Only 10 (8%) of the men had positive assays for pathogens such as *M. genitalium, T. vaginalis,* and *C. trachomatis.* However, 77% of subjects had evidence of 16S ribosomal DNAs, suggesting a role for previously undescribed microorganisms in chronic prostatitis–chronic pelvic pain syndrome. Urethral stricture may follow gonococcal urethritis or NGU. *N. gonorrhoeae* and *C. trachomatis* can infect the conjunctiva. Also, an oculogenital syndrome consisting of NGU and conjunctivitis may be seen in about 4% of patients with NGU[82]; it responds to standard therapy with tetracyclines and must be differentiated from reactive arthritis (see later discussion). Gonococcal and chlamydial infections in women are associated with pelvic inflammatory disease and its potential complications of tubal infertility, ectopic pregnancies, and chronic pelvic pain.

THERAPY

Specific forms of urethritis, including gonococcal, chlamydial, mycoplasmal, and trichomonal, should be treated as discussed in the appropriate chapters in Part III of this text. As a syndrome, NGU has been treated with a variety of regimens, but doxycycline and azithromycin are the current drugs of choice.[19]

Tetracyclines are usually prescribed for 7 days; there is little convincing evidence that full-dose regimens exceeding 7 days have any additional benefits.[83] Tetracycline hydrochloride is given in doses of 500 mg four times a day. The patient should be instructed to take the drug on an

empty stomach, not accompanied by milk or antacids. Alternatively, doxycycline can be administered in a dose of 100 mg orally twice daily for 7 days. This drug is highly effective, is well tolerated by patients, and can be taken with food. Twice-daily administration and fewer side effects are probably associated with better compliance. Inexpensive generic preparations are available. A doxycycline delayed-release 200-mg tablet administered daily for 7 days was as effective as twice-daily doxycycline in a randomized controlled trial for the treatment of chlamydial urethritis.[84] Doxycycline is the tetracycline of choice for treatment of NGU. Administration of doxycycline may be associated with photosensitivity reactions. Minocycline has no apparent advantages over doxycycline, and it produces dizziness in many patients.

Azithromycin is an azalide antimicrobial agent with a prolonged half-life that is active against *C. trachomatis.* A single 1-g oral dose is effective and is also more active than doxycycline against *M. genitalium.*[19]

Both doxycycline and azithromycin are highly effective and well tolerated. Generic doxycycline is inexpensive, but compliance is an issue, with the 7-day regimen not completed by patients in all instances.[85] Importantly, self-reported suboptimal adherence with a 7-day regimen of doxycycline was associated with microbiologic failure in the treatment of urethritis due to *U. urealyticum* and *C. trachomatis.*[86] Azithromycin may be more expensive, but compliance can be ensured if the drug is given under direct observation.

Erythromycin is as effective as tetracycline in chlamydial infections and is active against tetracycline-resistant ureaplasmas.[54] Erythromycin has the additional theoretical advantage of producing higher prostatic levels than those obtainable with tetracycline hydrochloride, and it may be used to re-treat patients whose symptoms are relieved by a tetracycline but who return after therapy is completed. Such patients may have a prostatic focus of infection that is not cured by tetracycline.[87] Gastrointestinal discomfort is a common and significant adverse effect of erythromycin therapy. Given the well-tolerated and effective options provided by azalide and tetracycline therapy, most clinicians no longer choose erythromycin. Recommended regimens include erythromycin base, 500 mg orally four times daily for 7 days, and erythromycin ethyl succinate, 800 mg orally four times daily for 7 days.[19] In addition to single-dose azithromycin therapy, a 5-day course of azithromycin (500 mg initially followed by 250 mg for 4 days) has been shown to be effective for both *M. genitalium* and *C. trachomatis* urethral infections.[88]

Fluoroquinolone antimicrobial agents have been evaluated in chlamydial urethritis and in syndromic NGU. Ciprofloxacin was ineffective, whereas ofloxacin (300 mg twice daily for 7 days) and levofloxacin (500 mg daily for 7 days) were effective.[19,89] In vitro studies suggest that moxifloxacin has activity against *C. trachomatis.*[90,91] Sulfonamides, including sulfisoxazole and trimethoprim-sulfamethoxazole, can also be used to treat chlamydial infections.

If all other therapies are contraindicated, an alternative treatment for chlamydial urethritis is amoxicillin. Several in vitro studies have shown amoxicillin activity against chlamydia, and clinical data suggest that it can be effective. Cure rates of *C. trachomatis* with amoxicillin treatment range from 58% to 80% in pregnant patients.[92] Therefore test of cure is necessary following amoxicillin therapy.

Even if the condition is untreated, symptoms of NGU may resolve; up to 70% of patients have complete resolution of symptoms within 6 months.[38] Resolution of symptoms does not mean that the infection is cured; asymptomatic patients may remain infected and infectious. Conversely the inflammatory response accompanying NGU may take some time to resolve even after the pathogens have been eliminated.

During treatment, the symptoms of NGU frequently resolve before the patient has completed the therapeutic regimen. Patients should be cautioned to complete the entire course of antibiotics because relapse may be more common if therapy is terminated early. To reliably differentiate a relapse from reinfection and to protect sexual partners, patients undergoing treatment for urethritis should be advised to refrain from coitus or to use condoms until both partners have completed their medication regimens and their symptoms have resolved.

Because coincident chlamydial infection is very common in men with gonorrhea and because of concerns about increasing gonococcal resistance to third-generation cephalosporins, the CDC[19] recommends that uncomplicated gonococcal urethritis should be treated with a combined regimen consisting of a single dose of a suitable cephalosporin (ceftriaxone, 250 mg intramuscularly in a single dose) followed by azithromycin (1.0 g orally in a single dose) (Table 107.4). This regimen has the advantage of providing effective single-dose therapy for gonorrhea and effective therapy for coincident, undiagnosed NGU. Disadvantages include increased cost and the potential for adverse reactions. It is also prudent to use a combination regimen to treat urethritis of undetermined origin. Fluoroquinolone-resistant strains of *N. gonorrhoeae* are widespread. Patients who have or may have gonorrhea should not be treated with fluoroquinolones unless the organism has been shown to be susceptible.[93]

TABLE 107.4 Therapy for Urethritis

DRUG AND DOSAGE	COMMENT
Ceftriaxone, 250 mg IM *plus* Azithromycin 1 g orally	For *Neisseria gonorrhoeae or Neisseria meningitidis* if documented by culture or NAAT, if suspected based on examination or history, or if gram-negative diplococci are seen on Gram stain.
Azithromycin, 1 g orally once *or* Doxycycline, 100 mg orally twice daily for 7 days	Appropriate for almost all forms of urethritis unless NAAT specifically does not demonstrate *Chlamydia trachomatis.* Azithromycin preferred for treatment of *Mycoplasma genitalium.*
Metronidazole 2 g orally once *or* Tinidazole 2 g orally once	If *Trichomonas vaginalis* has been demonstrated by light microscopy, culture, or NAAT or if these tests are not available when symptoms persist despite above-listed therapies.

IM, Intramuscularly; *NAAT,* nucleic acid amplification tests.

N. gonorrhoeae has demonstrated a consistent capacity to develop resistance and cross-resistance to previously effective antimicrobial agents. More recently a gradual but disturbing declining trend in the efficacy of cephalosporins has been noted.[94,95] Cefixime, previously recommended along with ceftriaxone for gonococcal treatment, should be used cautiously, if at all, as efficacy is no longer believed to be as reliable.[19] The CDC does not recommend cefixime as first-line therapy for gonorrhea due to reported treatment failures.[95] Suspected *N. gonorrhoeae* cephalosporin treatment failures should be reported to local public health authorities. Ongoing surveillance for emerging *N. gonorrhoeae* resistance is performed in the United States by the CDC-sponsored Gonococcal Isolate Sensitivity Project and by other public health organizations internationally. Globally there has been a gradual increase in minimal inhibitory concentrations of gonorrhea to ceftriaxone.[96–99] The World Health Organization Gonococcal Antimicrobial Surveillance Programme reported that rates of ceftriaxone resistance exceed 5% in several regions of Asia.[100]

Alternative therapeutic options are limited. Combinations with the fluoroquinolone gemifloxacin, 320 mg orally once, plus azithromycin, 2 g orally once, and gentamicin, 240 mg intramuscularly once, plus azithromycin, 2 g orally once, have been recommended as evidence-based therapies.[101] All elements in combination therapy for *N. gonorrhoeae* should be administered at the same time to achieve proper efficacy. New therapies, including solithromycin, zoliflodacin, and gepotidacin, are being evaluated at the present time and are at various stages of development.[100] In cases of *N. meningitidis* urethritis, patients were successfully treated for presumptive *N. gonorrhoeae* infection based on intracellular gram-negative diplococci. *M. genitalium* resistance to azithromycin and doxycycline has been reported worldwide. Moxifloxacin has been effective in some instances for urethritis refractory to these agents; however, fluoroquinolone resistance is now emerging.[102,103]

Patients who are receiving therapy for urethritis should be examined for other STDs and should be tested serologically for syphilis and HIV infection at the initial visit. An initial workup for trichomoniasis may be worthwhile in settings with a high prevalence of trichomoniasis in women. Direct microscopic examination of a urethral specimen for trichomonads is usually unrewarding, even if the patient can be seen before the first morning micturition. If the patient's urethritis has not

been cured by previous antibacterial therapy, or if symptoms or signs in the sexual partner suggest trichomonal infection, the patient's first-void urine sediment, an endourethral swab sample, or both can be examined with use of culture or NAAT. Empirical treatment for trichomoniasis may be warranted in such patients. Syndromic management of urethritis, in which men who have symptoms or signs of urethritis are treated with antimicrobial agents active against *N. gonorrhoeae* and *C. trachomatis* without any diagnostic studies, has been employed with success in resource-poor settings.[104]

In men whose symptoms and signs do not resolve or in whom clinical manifestations recur after appropriate treatment for urethritis, urethral Gram-stained specimens or first-void urine sediments should be examined to establish the existence of persistent urethritis. Symptoms and signs may persist in the absence of objective evidence of urethritis. Antimicrobial treatment in symptomatic men who do not have objective evidence of urethritis is of questionable value.[21]

In patients who initially receive and complete treatment for NGU but in whom urethritis is not eliminated by doxycycline or azithromycin, infection with *Trichomonas* or resistant *M. genitalium* or *U. urealyticum* should be suspected.[53,105] *M. genitalium* is the most likely etiologic agent for refractory NGU, especially if the patient was treated with doxycycline.[56,58] If not previously administered, 1 g of azithromycin can be attempted; if symptoms persist, the recommendation is to give moxifloxacin, 400 mg/day for 7 days.[19] Because these infections can be impossible to differentiate clinically, patients may be given empirical treatment with a single 2-g dose of metronidazole or tinidazole followed after 2 hours (to prevent gastrointestinal upset) by azithromycin, 1 g orally as a single dose.[19] It is important that sexual partners of patients receive the same regimen.

Some men report that their urethral symptoms disappeared while they were taking an antimicrobial agent but reappeared days to weeks after completion of therapy. Such recurrences with objective evidence of urethritis are seen in about 20% of patients with chlamydial NGU and in about 40% of patients with nonchlamydial infection. *M. genitalium* has been associated with recurrent or chronic NGU.[106]

Men with recurrent urethritis should be questioned closely about the possibility of reexposure, and attention should be given to ensuring simultaneous treatment of all sexual partners. If reexposure is likely, repeat treatment with the initial doxycycline or azithromycin regimen may be given. If the patient has not been reexposed, a recurrence of urethritis suggests the possibility that some pathogens remained in a relatively antibiotic-protected site. Prostatic involvement is common in NGU. It is possible that some men have a prostatic focus of infection. In men with repeated relapses, treatment with a 3-week course of erythromycin occasionally succeeds.[107] Patients whose relapses are not eliminated by these maneuvers should be referred for urologic evaluation to rule out anatomic abnormalities.[87] Such men probably are not infected with *Chlamydia* or *Ureaplasma*. About one-fourth of patients will be found to have a partial obstruction to urine flow, and about half of these will have urethral strictures.[87] These patients and their sexual partners do not appear to be at significant risk for infectious complications.[108] Long-term antimicrobial suppression is useful in this setting.[108]

Sexual partners of patients with sexually transmitted urethritis should receive treatment simultaneously. A woman who has been the sexual partner of a man with urethritis of undetermined origin should be given a regimen that is effective against gonococci, chlamydiae, and *M. genitalium*. A regimen combining a cephalosporin with azithromycin, as described previously, is suitable. In one study, patient-delivered partner treatment was more effective in treating partners of men who had urethritis than standard partner referral.[109] Asymptomatic male sexual partners of women known to have gonorrhea, chlamydial infection, or trichomoniasis should receive treatment even in the absence of abnormalities on direct microscopic examination.

THERAPY FOR SEXUAL PARTNERS OF MEN WITH NONGONOCOCCAL URETHRITIS

Female sexual partners of men who have urethritis are often infected with one or more of the causative microorganisms. Although infected women are often asymptomatic, the organisms are far from benign. *C. trachomatis* is a cause of acute salpingitis. Additionally, infants born to infected women may develop chlamydial conjunctivitis or pneumonia. *T. vaginalis* is an important cause of vaginitis,[14] and *M. genitalium* has been implicated as a cause of cervicitis.[51] Asymptomatic women with these infections are undoubtedly a reservoir for recurrent NGU. These considerations support the routine treatment of female sexual partners of men with NGU.

REACTIVE ARTHRITIS

Some cases of NGU appear as one element of reactive arthritis (formerly known as Reiter syndrome), which also includes arthritis, uveitis, and, often, lesions of the skin and mucous membranes.[110] The syndrome complicates 1% to 2% of cases of NGU[111] and is believed to be the most common peripheral inflammatory arthritis in young men.[112] Its pathogenesis is unclear, but it probably represents an abnormal host response to any of a number of infectious agents.[113] The syndrome is reported infrequently in women. The idiosyncratic nature of the host's response is supported by a strong correlation between the development of reactive arthritis and the presence of the human leukocyte antigen (HLA)-B27 histocompatibility antigen. This antigen has been found in 90% to 96% of patients with reactive arthritis,[114] and it has been related to uveitis and sacroiliitis.[111] Although possibly providing a clue to pathogenesis, the presence of this antigen is not diagnostic.

The inciting infection is of two types. Sexually acquired reactive arthritis (SARA) may occur after sexually transmitted urethritis.[115] Most cases in North America and Europe occur in sexually active young people.[116] Many cases occur after contact with a new partner, and some cases have been epidemiologically linked.[111] In one series, 9% of cases occurred after gonococcal urethritis, although 50% of affected patients subsequently developed PGU.[117] *C. trachomatis* is strongly implicated in the pathogenesis of SARA.[118,119] It has been recovered from the urethras of 50% of patients with SARA and from most of the men who had signs of urogenital inflammation at the time of examination.[120,121] Antibodies to *C. trachomatis* have been detected in about half of patients with SARA, and *Chlamydia*-specific cell-mediated immunity occurs in most patients with SARA.[121,122] Chlamydiae were isolated from synovial biopsy specimens in 15 of 29 patients from a number of small series and from a smaller proportion of synovial fluid specimens.[123] Chlamydial nucleic acids have been identified in the synovial membranes,[124] and chlamydial elementary bodies have been observed in joint fluid.[125] Rates of reactive arthritis have been declining in some reports despite increasing rates of *C. trachomatis* infection.[126] SARA has been reported with lymphogranuloma venereum.[127] *M. genitalium* infection has preceded SARA.[128,129] Attempts to isolate or identify mycoplasmas in affected joints have not been successful.[123]

Reactive arthritis also occurs after bacterial gastroenteritis, and it has been repeatedly described after infection with *Salmonella, Shigella, Yersinia,* or *Campylobacter.*[111,112,117] A few cases suggest that reactive arthritis may occur after antibiotic-associated colitis[130] or cryptosporidiosis.[131] Postdysenteric reactive arthritis has been reported in about 1% of patients after epidemics of gastrointestinal infection; it is considerably more common among patients who are HLA-B27 positive. Short peptides shared by HLA-B27 and enteric pathogens have raised the question of a contribution of molecular mimicry to pathogenesis.[132] Antibodies reacting with *Yersinia* proteins appear in the sera of many patients with reactive arthritis.[133]

Clinically, reactive arthritis after genital infection is indistinguishable from reactive arthritis occurring after bacterial gastroenteritis; indeed, 12% to 80% of patients with postdysenteric reactive arthritis have genital symptoms.[111,134] The age-specific and sex-specific attack rates, however, are different; 94% to 99% of cases of reactive arthritis after sexually transmitted infections occur in men. However, up to 10% of cases of postdysenteric reactive arthritis occur in women.[116] The syndrome has also been reported in sexually inexperienced children.[116]

Reactive arthritis is encountered with some frequency in HIV-infected individuals.[135] It is said to be the most common rheumatologic complication of acquired immunodeficiency syndrome. The spectrum of clinical manifestations is similar to that in other patients, but the arthritis and mucocutaneous lesions are more severe and may require more intensive therapy.

Clinical Manifestations

NGU is the initial manifestation of reactive arthritis in 80% of patients.[111,112] As with other forms of NGU, it usually occurs within 14 days after sexual exposure. Urethritis may be mild and may go unnoticed by the patient, being detectable only by physical examination performed before the first morning micturition. Gonococcal urethritis sometimes precedes reactive arthritis,[117] but coinfection with an agent of NGU is difficult to rule out. The urethral discharge may be purulent or mucopurulent, and patients may or may not report dysuria. Accompanying prostatitis, usually asymptomatic, has been described by some authors.[112,134,136] Cystitis without urethritis also has been reported and may be a manifestation, particularly in women.[134] Cervicitis has been described in women presenting with reactive arthritis.[137] The other features of reactive arthritis develop 1 to 5 weeks after the onset of urethritis.[134] Arthritis begins within 4 weeks after the onset of urethritis in 80% of patients,[111] but it precedes urethritis in about 15%.[116] The knees are most frequently involved, followed by the ankles and small joints of the feet. Sacroiliitis, either symmetrical[134] or, more frequently, asymmetrical,[116,136] develops in up to two-thirds of patients. It is more common in patients with the HLA-B27 antigen. Ankylosing spondylitis, which occurs in only about 1% of the general population, complicates a significant minority of cases of reactive arthritis,[111,138] and back pain is reported by 60% of all patients.[112] Many patients with reactive arthritis and the HLA-B27 antigen develop ankylosing spondylitis,[138] which is rare in patients without the antigen. Calcaneal spurring may be seen in one-fourth of patients with reactive arthritis[111,136] and may produce heel pain. A dactylitis resulting in sausage-shaped swelling of the digits is also characteristic.[116] Arthritis is the most persistent feature of the syndrome; it may last for months to years after other manifestations have disappeared.[116,134]

Mild bilateral conjunctivitis, iritis, keratitis, or uveitis is sometimes present but often lasts for only a few days.[134,136,139] In contrast to the conjunctivae in direct infection with *C. trachomatis,* the inflamed conjunctivae in reactive arthritis do not manifest follicular hypertrophy. Uveitis is usually anterior, acute, and unilateral.

Dermatologic manifestations occur in up to 50% of patients.[111,112] The initial lesions are waxy papules, which often display a central yellow spot; they occur most frequently on the soles and palms[134] and with decreasing frequency on the nails, scrotum, scalp, and trunk. The papules epithelialize and thicken to produce keratoderma blennorrhagicum in 10% to 25% of the patients.[112] Circinate balanitis is usually painless and occurs in 25% to 40% of all patients.[111,112,134] Circinate and ulcerative vulvitis also are described.[140] Painless erosions on the dorsum of the tongue and fauces occur most commonly with the initial episode and less frequently with recurrence. Incomplete reactive arthritis, consisting of urethritis and arthritis or arthritis alone, has been reported.[112,141]

The initial episode of reactive arthritis usually lasts 2 to 6 months, but episodes lasting for 1 year have been described.[112,134,136] Most patients feel completely well after the attack subsides, but the disease recurs in many cases, at a rate of about 15% in each 5-year period after the initial attack.[111,112,116,125] During recurrence, the genital symptoms are usually less marked and may be entirely absent.[142] More than half of patients have active disease 15 to 20 years after the initial episode,[112,138,143] the risk for residual disease being higher among patients with the HLA-B27 antigen. Almost 50% of affected individuals develop some degree of permanent disability.[138] Rare complications of reactive arthritis include pericarditis, myocarditis, first-degree atrioventricular block, and aortic insufficiency.[134,136]

Laboratory Findings

Anemia is common,[112] and the erythrocyte sedimentation rate is elevated in about 50% of patients.[116] Findings in fluid recovered at the same time from different joints may be dissimilar.[134] Synovial fluid usually contains 1000 to 200,000 white blood cells/mL, of which more than two-thirds are PMNs.[134] The glucose level in joint fluid is low in about 50% of affected joints.[134] Synovial biopsy specimens reveal nonspecific inflammatory changes.

Therapy

Treatment of reactive arthritis is controversial.[144] Because of the possibility that the inciting infection may be sexually transmitted NGU, standard antichlamydial therapy is recommended[143] and has been claimed by some authorities to reduce or eliminate urethritis.[145] Others, however, have seen no effect on the arthritis or on the overall course of the disease.[143] The relative safety of antichlamydial therapy and the frequency with which chlamydiae are isolated from patients with reactive arthritis make such treatment reasonable. Among a population in Greenland with a high prevalence of HLA-B27, treatment of patients who had urethritis or cervicitis with a tetracycline or erythromycin was associated with a lower incidence of subsequent arthritis than was treatment with penicillin or no treatment at all.[146]

Long-term antichlamydial treatment (e.g., with a tetracycline for 3 months) has been suggested, and its use was supported by the results of a double-blind, placebo-controlled trial that demonstrated an ameliorating effect on *Chlamydia*-associated, but not on enteropathogen-associated, disease.[147] The effectiveness of long-term tetracycline therapy in other arthritides[148] raises the question of whether the drug is working through an antibacterial effect on persistent, viable microorganisms or through an antiinflammatory action. That the tetracyclines are more effective in *Chlamydia*-associated disease than in other reactive arthritides suggests the former.

Administration of nonsteroidal antiinflammatory drugs (NSAIDs) is the most effective treatment.[112] Indomethacin or tolmetin is favored by some workers, and all these agents are superior to salicylates or corticosteroids. Sulfasalazine may be beneficial for patients whose symptoms do not respond to a nonsteroidal antiinflammatory drug. Cytotoxic agents such as methotrexate[149] or immunosuppressive agents such as infliximab[150] may be of value in recalcitrant cases.

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The complete reference list is available online at Expert Consult.

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108 Vulvovaginitis and Cervicitis

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SHORT VIEW SUMMARY

Definition
- Vulvovaginitis and cervicitis include infectious and noninfectious conditions involving the vulva, vagina, and cervix.

Epidemiology
- Trichomoniasis is a sexually transmitted condition.
- Bacterial vaginosis (BV) and vulvovaginal candidiasis (VVC) are not classic sexually transmitted diseases but seldom occur in sexually inexperienced women.
- Vulvar pain syndrome and desquamative inflammatory vaginitis (DIV) are not sexually transmitted.
- Cervicitis may be sexually transmitted or idiopathic.

Microbiology
- Trichomoniasis is caused by *Trichomonas vaginalis*.
- Candidiasis is caused by *Candida albicans* and other fungal species.
- Bacterial vaginosis is associated with a complex bacterial microbiota.
- Infectious cervicitis is usually caused by Neisseria gonorrhoeae, Mycoplasma genitalium, or Chlamydia trachomatis.

Diagnosis
- Trichomoniasis and cervical infections due to *N. gonorrhoeae*, *M. genitalium*, and *C. trachomatis* can be diagnosed by identifying the causative organisms with use of culture or nonculture methods, of which nucleic acid amplification testing is the most accurate.
- BV is diagnosed using clinical criteria, including vaginal pH, odor produced when potassium hydroxide is added to vaginal fluid, and detection of "clue cells" when vaginal fluid is examined microscopically.
- VVC is diagnosed clinically and by the identification of *C. albicans* or other fungal species in cultures of vaginal fluid.
- DIV is diagnosed by the clinical appearance of the vagina and the identification of leukocytes and parabasal cells in wet preparations of vaginal fluid.

Therapy
- Trichomoniasis is treated with the oral administration of metronidazole or tinidazole.
- BV is treated with a 7-day course of oral metronidazole or with preparations for intravaginal use that contain metronidazole or clindamycin.
- VVC is treated with oral fluconazole or with preparations for vaginal use that contain nystatin, miconazole, or other antifungal agents.
- DIV is best treated with intravaginal clindamycin.
- Intravaginal administration of boric acid or corticosteroids provides symptomatic relief for DIV.

Prevention
- Judicious choice of sexual partners and regular use of condoms is preventive.

Vulvovaginal symptoms are common and frequently result in encounters of patients with the health care system, including use of folk remedies, purchase of over-the-counter (OTC) pharmaceuticals, and presentation to health care providers. In one survey[1] of female college graduates with a median age of about 30 years, almost 70% reported at least one lifetime physician-diagnosed and treated vaginal yeast infection; in addition, 29% had been treated for bacterial vaginosis (BV) and 26% for trichomoniasis. Greater than 20% of the women had been treated for a vaginal yeast infection within the prior year.

Genitourinary symptoms in women tend to lack specificity. All women have vaginal secretions, but their ability to discriminate normal from abnormal secretions is often imprecise. Similarly, vulvar discomfort is fairly common and may result from a variety of infectious and noninfectious causes. This chapter discusses vaginal discharge and vulvitis separately, with the understanding that there is considerable overlap between these syndromes and that a patient whose symptoms appear to represent one syndrome may ultimately have a quite different diagnosis.

VAGINAL SECRETIONS

The normal vaginal secretions are a physiologically important biomass. Vaginal cells contain glycogen and are continually shed into the lumen of the vagina. As the cells autolyze, glycogen depolymerizes to glucose, which serves as an energy source for bacteria known as lactobacilli. Data reported by Ravel and associates[2] demonstrated that the vaginal bacterial communities of asymptomatic North American women clustered into five groups: four were dominated by *Lactobacillus crispatus*, *Lactobacillus jensenii, Lactobacillus iners,* or *Lactobacillus gasseri,* whereas the fifth had lower proportions of lactobacilli and higher proportions of strictly anaerobic organisms. Lactobacilli metabolize glucose to lactic acid, which results in a normal vaginal pH of about 4.0.

In the studies of Ravel and associates[2] the vaginal communities of women whose microbiota was dominated by *L. jensenii* and those with higher proportions of strictly anaerobic bacteria had higher mean pH levels than the other groups. In addition, blacks and Hispanics had higher mean vaginal pH levels than whites and Asians.

The vagina is not sterile, and many species of bacteria can be isolated from vaginal specimens from healthy women, including *Prevotella, Megasphaera, Gardnerella,* and *Atopobium* spp., but lactobacilli usually dominate the vaginal microbiota. Indeed, the predominant cells in the vaginal secretions of most normal women are lactobacilli and vaginal epithelial cells (Fig. 108.1).

In addition to producing lactic acid, lactobacilli may also produce hydrogen peroxide, which is bactericidal alone and highly bactericidal in combination with physiologic amounts of myeloperoxidase and chloride.[3] Loss of the normal *Lactobacillus*-dominated vaginal microbiota increases the likelihood of exogenous infection after exposure to sexually transmitted pathogens,[4] as well as the risk for endogenous infection in association with pregnancy and gynecologic surgery.[5]

Therefore the normal vaginal secretions are a heterogeneous suspension of vaginal epithelial cells and lactobacilli in fluid that emanates from the cervix and vaginal walls (Fig. 108.2). The secretions have a pH of 3.5 to 4.6, are odorless, and do not cause itching or irritation. This acidic environment inhibits the growth of many pathogenic organisms. The normal secretions are clumpy and tend to remain in the vagina, although in some women egress of normal secretions may require use of a perineal pad. Characteristics of normal vaginal secretions are listed in Table 108.1.

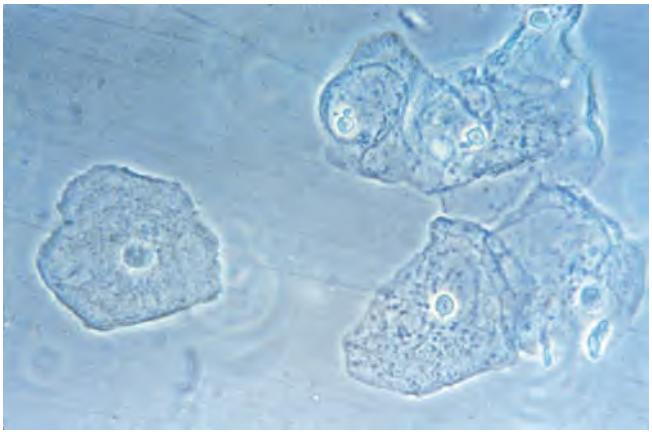

FIG. 108.1 Healthy vaginal secretions. Normal vaginal secretions as seen in a suspension of vaginal secretions in 0.9% sodium chloride. Vaginal epithelial cells and lactobacilli are the primary cells seen.

FIG. 108.2 Healthy vaginal secretions on a speculum. Normal vaginal secretions on a plastic vaginal speculum. The secretions are off-white and heterogeneous.

TABLE 108.1 Characteristics of Normal Vaginal Secretions

Heterogeneous suspension of desquamated vaginal epithelial cells in water
Lactobacilli dominate the microbiota
pH of 3.5–4.6
Odorless
Do not cause itching or irritation
Usually do not soil underclothing

An appreciation of what is normal is important in dealing with patients who report an abnormal discharge. A significant minority of such patients have normal secretions. These women may have a large volume of normal secretions, relaxation of the introitus after childbirth that allows outflow of normal volumes of normal secretions, or heightened awareness of a normal amount of physiologic secretions, often as a result of other genitourinary symptoms, such as vulvar discomfort. The volume of normal secretions may increase during pregnancy, during use of hormonal contraceptive agents, and at midmenstrual cycle

Patients with a normal or physiologic vaginal discharge usually have a history of multiple self-directed or clinician-directed treatments with a wide array of topical and systemic antibacterial and antifungal agents. Recognition of the normalcy of the secretions is important so that the patient can be reassured that her secretions are normal and so that diagnostic and therapeutic attention can be focused on associated conditions, if any, that may be present.

Important characteristics of patients who present with normal vaginal secretions are listed in Table 108.2. Notable characteristics include chronicity, absence of odor, absence of vulvar discomfort (unless there is unrelated vulvitis), many unsuccessful visits to a variety of different health care providers, and many ineffective treatments.

On close questioning a number of these patients do not have sufficient external flow of vaginal secretions to stain their clothing or to require use of a perineal pad. They appreciate what they perceive to be abnormal secretions by extracting normal secretions with use of their index finger. This *finger test* is an important historical clue that the woman has normal secretions.

In addition to normal secretions, the differential diagnosis of vaginal discharge primarily includes three conditions (trichomoniasis, vulvovaginal candidiasis [VVC], and BV), an idiopathic condition known as desquamative inflammatory vaginitis (DIV), cervicitis (both infectious and noninfectious), and vulvovaginitis associated with estrogen deficiency (Table 108.3).

TABLE 108.2 Characteristics of Patients Who Report Vaginal Symptoms but Are Found to Have Normal Vaginal Secretions

Chronicity of symptoms
Many prior visits to health care practitioners
Multiple ineffective treatments with vaginal and oral antimicrobial agents
Absence of odor
Absence of itching and irritation
Minimal, if any, staining of clothing

TABLE 108.3 Differential Diagnosis of the Abnormal Vaginal Discharge

Normal (physiologic) vaginal secretions
Vaginal infections
Trichomoniasis
Vulvovaginal candidiasis
Bacterial vaginosis
Desquamative inflammatory vaginitis
Cervicitis
Infectious
Noninfectious
Estrogen deficiency

TABLE 108.4 Most Pertinent History From Patients With Vulvovaginal Symptoms

General Gynecologic History
Menstrual history
Pregnancies
Sexual preference
Contraception
Sexual relationships
Prior infections
General medical history
Allergies
Diabetes
Malignancies
Immunodeficiency
Symptoms of Vulvovaginitis
Discharge
Odor
Vulvar discomfort
Dyspareunia

APPROACH TO THE PATIENT

History

The etiologic diagnosis of vaginitis depends on a careful evaluation of the history, a physical examination, and immediate laboratory tests. Historical features are relatively nonspecific,[6] but they may direct clinical suspicion toward certain causes. If at all possible, the history should be obtained with the patient in the sitting position and before she has disrobed.

The medical history (Table 108.4) should include all of the usual gynecologic parameters, including menstrual history, pregnancies,

contraception, sexual preference, past and current sexual relationships, and prior genitourinary infections. In addition, the patient should be asked about underlying medical conditions, such as allergies, diabetes, malignancies, and immunodeficiency syndromes (primarily human immunodeficiency virus [HIV] infection), that might be associated with or influence vulvovaginal disease. Recent use of antimicrobials for any reason may result in disruption of normal vaginal microbiota and therefore cause a vaginal discharge. Patients should be asked also about any possible mechanical or chemical irritants use, such as scented panty liners, soaps, latex condoms, and so forth, that may cause subacute and chronic vaginal symptoms attributed to infections.[7]

Age

Neonates can acquire trichomonal or candidal vulvovaginitis during passage through an infected birth canal, which would argue for treating these infections in pregnant women before term. Neonatal vaginal thrush responds promptly to topical antifungal medications. Neonatal trichomoniasis can be treated with metronidazole. After the neonatal period a vaginal discharge is abnormal and should prompt a thorough examination. Vaginal candidiasis is rare in prepubescent girls. Prepubescent vaginal epithelium is thin, and the entire vagina is susceptible to infection with *Neisseria gonorrhoeae.* Gonococcal vulvovaginitis often causes profuse vaginal discharge. The diagnosis of a sexually transmitted disease (STD) in a young girl should raise the strong suspicion of child abuse, although some agents have been transmitted to children in the absence of frank sexual contact.[8] Patients in the sexually active years are more likely to have physiologic secretions or infectious vaginitis. Postmenopausal women are more likely to have atrophic vaginitis with vaginal dryness and dyspareunia.

Mode of Onset

An abrupt and identifiable time of onset of symptoms suggests infection. Vaginal discharge associated with neoplasia, estrogen depletion, or a foreign body often has a subacute onset, with symptoms progressing over a period of weeks.

Quantity of Discharge

The amount of discharge is highly variable in all conditions. Patients with VVC often have scanty discharge or no discharge at all. Atrophic discharges are commonly scanty unless infection has supervened.

External Irritation

Physiologic discharge is rarely associated with vulvar or perineal discomfort. Pruritus with a scant or absent discharge is frequently seen in candidiasis. External discomfort is an infrequent complaint in BV. Severe episodic perineal pain that sometimes prevents urination suggests herpes simplex virus (HSV) infection, which affects the labia but usually spares the vagina. Chronic discomfort (often interfering with sexual activity) should prompt consideration of a noninfectious vulvitis, such as vulvar vestibulitis.

Odor

Vaginal odor in the absence of other symptoms is the initial complaint in many cases of BV. A feculent odor may accompany anaerobic superinfection of genital lesions, or it may be noted in the presence of a foreign body or enterovaginal fistula.

Abdominal Pain

Abdominal discomfort is rare in uncomplicated vulvovaginitis, except for some cases of trichomoniasis. Women who complain of abdominal pain should be examined for evidence of urinary tract infection (UTI) and pelvic inflammatory disease.

Sexual History

Exposure to a new sexual partner increases the likelihood of STD. A history of genital symptoms in a sexual partner is helpful diagnostically. Women who have sex with women are at risk of bacterial vaginosis.[8] And although bacterial vaginosis is not considered a typical STD, women who are not sexually active do not suffer with this condition.

Other Diseases

Diabetes mellitus, acquired immunodeficiency syndrome, malignancy, and the treatments thereof, and possibly hypoparathyroidism, increase the risk for candidal vaginitis. Diseases known to impair host defenses may predispose to otherwise rare infections. Drugs used in the treatment of other diseases may predispose to vaginal infection.

Medications

Systemic or local medications may influence vaginal infection. Antibiotics that are active against the normal bacterial microbiota of the vagina predispose to candidal vaginitis.[9] Patients who are taking corticosteroids or oral contraceptives are at increased risk for development of VVC. Local medications, including vaginal douches, rarely produce a chemical vaginitis; douching immediately before examination makes diagnosis difficult.

The commencement of oral contraceptive use may be associated with increased physiologic discharge.

Physical Examination

If the patient has not had recent medical care, a general physical examination can be performed. At the least the patient's breasts should be examined if she has not had a professional breast examination during the past year. Similarly, a mammogram should be ordered if the patient's age or history dictate that one is indicated.

With the patient supine on the examining table, the pubic hair should be examined for the presence of crab lice or nits. The inguinofemoral areas should be palpated for adenopathy. Suprapubic and lower abdominal tenderness or masses can be sought by palpation.

The gynecologic examination (Table 108.5) requires adequate light. Magnification is helpful and is best provided by a colposcope. Providing the patient with a mirror allows her to participate in the examination and is useful for clarifying the location of symptoms and demonstrating important findings to the patient.

With the patient in the lithotomy position, the external genitalia should be carefully inspected. The patient should be asked to point to any areas of external itching, irritation, or other discomfort. Localization of discomfort to vulvar skin or vestibular mucosa provides useful information. The appearance of the vulvar skin and vestibular mucous membranes should be noted, with careful attention to ulcers or other discontinuity of the skin or mucosa, mucosal erythema, and visible secretions. Diffuse perineal erythema may accompany candidiasis. Diffuse reddening with small satellite lesions, usually papular or papulopustular, suggests candidiasis. The degree of perineal irritation is quite variable with all infections, but severe perivaginal irritation is uncommon with BV. Labial edema may accompany severe irritation, especially in VVC, trichomoniasis, or dermatitis.

Careful examination of all the extravaginal surfaces may reveal lesions of genital herpes, syphilis, condyloma acuminatum, molluscum contagiosum, scabies, or vulvar vestibulitis.

TABLE 108.5 Principles for the Genital Examination of the Patient With Vulvovaginal Symptoms

- Adequate illumination
- Magnification, if possible
- Give the patient a mirror
- Inspect the external genitalia
  - Lesions
  - Mucosal erythema
- Examine the vaginal mucosa
  - Erythema
  - Lesions
  - Secretions
- Examine the cervix
  - Ectropion
  - Lesions
  - Erythema
  - Endocervical secretions
- Collect vaginal and cervical specimens
- Bimanual examination

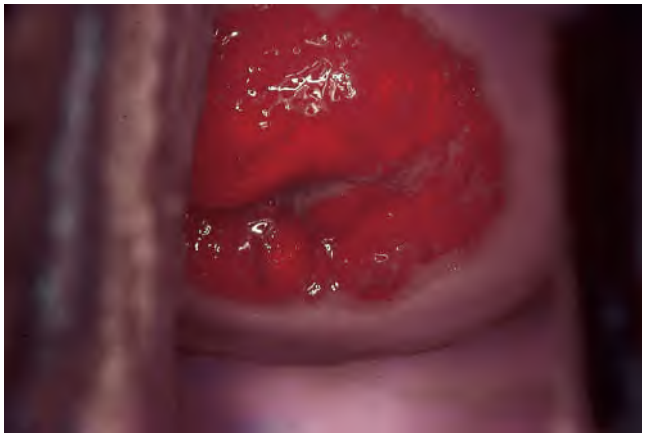

FIG. 108.3 Healthy cervix. Normal cervix with a normal ectropion.

TABLE 108.6 Specimens Obtained During the Gynecologic Examination

Vaginal secretions
pH
Whiff test
Saline wet preparation
Potassium hydroxide wet preparation
Cultures or nonculture tests
Neisseria gonorrhoeae
Chlamydia trachomatis
Candida spp.
Trichomonas vaginalis
Cervical cytologic examination (if not documented within the currently recommended time frame)

By spreading the labia with the gloved hand, one may examine the urethral meatus. The urethra may be gently stripped with a finger placed inside the vagina. Urethral discharge is not a common finding, but, if delivered, such material should be examined microscopically and cultured. The introitus and the internal surfaces of the labia minora should be examined for lesions. Vaginal discharge is sometimes observed on the labia or flowing onto the perineum. Such copious discharge is usually associated with trichomoniasis or BV but may accompany other infections.

A speculum is then inserted to expose the cervix and vaginal mucosa. A small-sized speculum is adequate for most patients and minimizes discomfort for patients who have introital lesions. A small amount of lubricant facilitates insertion without compromising the quality of the microbiologic samples to be collected. The vaginal and cervical mucosa should be inspected with attention to erythema and lesions. An ectropion, if present, should be noted (Fig. 108.3). The vaginal secretions should be described, as should any secretions emanating from the endocervical canal or from an ectropion.

Diagnostic Evaluation

Specimens obtained during the examination are listed in Table 108.6. Vaginal pH should be measured. A sample of vaginal material should be collected from the lateral vaginal wall with use of a cotton-tipped applicator. Care should be taken to avoid contamination with endocervical secretions. The collected vaginal secretions are applied to a strip of pH paper and compared with the standard chart provided by the manufacturer (Fig. 108.4). A high pH in premenopausal women indicates infections such as BV and trichomoniasis, whereas in postmenopausal women, pH is usually high due to lack of estrogen vaginal secretions, and its measurement become less useful in diagnosing infection.

A sample of vaginal secretions is then examined. The specimen may be prepared in several ways. A swab of vaginal secretions may be agitated in a tube containing about 0.5 mL of normal saline to form a suspension. Alternatively, a plastic transfer pipette may be used to introduce 2 to 3 mL of normal saline solution into the posterior fornix. The saline solution is mixed with the vaginal secretions by aspiration and reaspiration of the solution, and the resultant suspension of vaginal material is placed into a small tube.

FIG. 108.4 Testing for pH. Examination of vaginal secretions for pH with use of pH paper.

The suspension is then examined for odor (whiff test) by placing a drop on a microscope slide, adding a drop of 10% potassium hydroxide (KOH), and smelling the resultant mixture. Normal secretions have no odor. A fishy odor is indicative of BV, due to metabolism of vaginal peptides into a variety of amines that are volatile and malodorous, as well as increased vaginal transudation and squamous epithelial cell exfoliation.

A drop of the suspension of vaginal material is placed on a microscope slide, and a coverslip is added. This *wet mount* should be examined within 10 to 20 minutes of collection under high power with a bright-field microscope. Phase-contrast microscopy provides an excellent means of evaluating vaginal wet mounts. The relative numbers of epithelial cells and polymorphonuclear neutrophils (PMNs) should be noted. Because PMNs are present in physiologic endocervical discharge that collects in the vagina,[10] small numbers of PMNs may be observed in the vaginal material recovered from healthy women. A finding of more PMNs than epithelial cells in a vaginal wet preparation should raise suspicion for cervical or vaginal inflammation. Observation of relatively few PMNs does not rule out vaginal infection, however. Vaginal candidiasis can produce a discharge that contains only small numbers of PMNs. The relative absence of PMNs is characteristic of the discharge of BV.[11] In fact, the finding of many PMNs in the vaginal discharge of a patient with BV should prompt a search for simultaneous infection, such as trichomoniasis, gonorrhea, or chlamydial cervicitis. Pseudohyphae suggest vaginal candidiasis, but often only moderate or even very small numbers of yeast cells are seen in this condition. Indeed, some patients with VVC have organisms identified only by culture. The wet preparation should be scanned for motile trichomonads.

Normal squamous epithelial cells have transparent cytoplasm and small nuclei. Immature (parabasal) cells are smaller and have larger nuclei. Epithelial cells covered with tiny coccobacillary forms are called *clue cells* and are associated with BV. Clue cells are best recognized by observing the edges of epithelial cells, which may be obscured by the adherent coccobacilli. Some cells are so heavily encrusted that the nuclei are obscured. Trichomonads are best recognized by their characteristic twitching motility. The flagellae and undulating membrane may be observed by careful focusing of the microscope and adjustment of the light source. Trichomonad motility may be improved by gentle warming of the preparation. The wet mount is negative in about 38% of the women with trichomoniasis[12] (see Chapter 280), so a negative wet mount does not rule out this infection, particularly in asymptomatic women.

The bacterial microbiota can be assessed on the wet mount. Normal vaginal microbiota consists of a sparse population of bacilli. In BV the predominant organisms are tiny coccobacilli. Spermatozoa may be observed as long as 10 days after the last coitus, but motile sperm suggest sexual contact within the preceding 24 hours.[13]

Combining a drop of 10% KOH with the vaginal material on a microscope slide and applying a coverslip destroys cellular elements but leaves the bacteria and fungi unscathed, enhancing the capacity to diagnose VVC. The KOH preparation cannot be used for microscopic diagnosis of trichomoniasis or BV.

A Gram stain of vaginal material is somewhat less useful than the wet mount for differential diagnosis. Although *Candida* spp. are readily

recognized on the Gram-stain smear, trichomonads are difficult to identify. Normal vaginal microbiota consists primarily of gram-positive bacilli, which are mostly lactobacilli. In BV the normal microbiota is replaced by sheets of gram-variable coccobacilli, which often overlie the surface of epithelial cells. Women with VVC sometimes have large numbers of budding yeasts and pseudohyphae. The Gram stain is negative in many women from whom *Candida* can be cultured.[14]

Material recovered from the endocervix can be Gram stained. Normal cervical discharge usually contains moderate numbers of PMNs, and their presence is not necessarily an indication of infection.[10] The presence of large numbers of PMNs suggests cervicitis. Gram-negative, intracellular diplococci accurately diagnose gonorrhea (see Chapter 212), but extracellular diplococci are less predictive. The cervical Gram stain is positive in only about 60% of women with cervical gonorrhea. Therefore a negative Gram stain does not rule out this infection.[14]

Before the speculum is removed, specimens are obtained for examination for *N. gonorrhoeae, Chlamydia trachomatis, Mycoplasma genitalium,* and *Trichomonas vaginalis* with use of culture or nonculture methods such as nucleic acid amplification tests (NAATs). Vaginal cultures for yeast are useful to exclude fungal infection, for which the wet preparation is insensitive,[15] and to identify non–*albicans Candida* spp. Trichomonads can be sought by inoculating selective liquid media, such as the modified Diamond medium, if trichomoniasis is a diagnostic possibility.[16] Trichomonas culture is labor intensive and expensive and is not routinely performed. Sensitive and specific antigen assays are available. Finally, a cervical cytologic smear should be obtained if such an examination cannot be documented within the currently recommended time frame. Relying on the patient's history of cervical cytologic examinations is risky, because some women assume that all gynecologic examinations include a Papanicolaou (Pap) smear.

Bimanual examination for adnexal tenderness and masses should be a part of the evaluation. Adnexal tenderness is sufficiently uncommon with local vaginal infections that its presence suggests salpingitis.

TRICHOMONIASIS

Epidemiology

Trichomoniasis is one of the three most common causes of vaginal complaints, along with BV and *Candida* vulvovaginitis. Trichomoniasis prevalence is difficult to determine because it is not reported to public health authorities. In a most recent study prevalence of *T. vaginalis* was 26% among symptomatic women, 6.5% in asymptomatic patients screened, and 29% in HIV-infected women.[17]

Etiology and Pathogenesis

Trichomoniasis is caused by the protozoan *T. vaginalis.* It is a classic exogenous sexually transmitted infection (STI), such as gonorrhea and chlamydial infection. The organism is not normally present in the vagina. Transmission almost always occurs through sexual contact. After an incubation period of a few days, patients develop a purulent discharge associated with varying degrees of vulvar irritation, dysuria, and dyspareunia (Table 108.7). An abnormal odor is often present, usually signifying concomitant BV.

Diagnosis

Examination is notable for vulvar, vestibular, and vaginal erythema and a purulent vaginal discharge (Fig. 108.5). A minority of patients manifest characteristic mucosal capillary dilation, which gives the mucosa a *strawberry* appearance. Vaginal pH is almost always higher than 4.5. A positive whiff test is not unusual. The vaginal wet preparation contains an abundance of leukocytes and motile flagellated trichomonads (Fig. 108.6). In experienced hands the wet preparation is only 60% to 70% sensitive in symptomatic patients.[18] Because the organisms remain motile for 10 to 20 minutes after collection of the sample, fixation and staining is not useful.

The organism can be cultivated by inoculating a liquid medium, such as the modified Diamond medium[16] or InPouch TV (Biomed Diagnostics, White City, OR).[19] After incubation, aliquots of the liquid medium are examined daily for motile trichomonads. Culture improves the diagnostic yield, especially in asymptomatic patients. These tests are not widely available and take up to 7 days to obtain result. Before the advent of molecular testing and direct antigen assays, culture was the gold standard for detection of *Trichomonas.*

Nonculture antigen detection tests approved by the US Food and Drug Administration (FDA) include the OSOM *Trichomonas* Rapid Test (Sekisui Diagnostics, Cambridge, MA), which can be used as a point-of-care test, and the Affirm VPIII (Becton Dickinson, Sparks, MD). These tests have sensitivity that approaches that of culture.[19,20] Sensitive and specific NAATs have become the gold standard for diagnosis of *T. vaginalis,* including the APTIMA *T. vaginalis* Assay (Hologic Gen-Probe, San Diego, CA).[21,22]

A wet preparation diagnostic of trichomoniasis is highly specific because of the characteristic motility of the organisms. Diagnostic tests in which the organisms are no longer motile may lack specificity. A common clinical problem is the woman with no epidemiologic evidence for a sexually transmitted condition who has trichomonads visualized on a cervical cytologic examination.[23] In some of these cases the cytologist may have misread the smear. For such a patient the clinician should obtain confirmation of the diagnosis of trichomoniasis, by wet preparation or culture (or both), before initiating treatment and before embarking on a potentially disruptive epidemiologic investigation.

TABLE 108.7 Symptoms of Trichomoniasis

Purulent vaginal discharge
Vulvar irritation
Dysuria
Dyspareunia
Abnormal vaginal odor

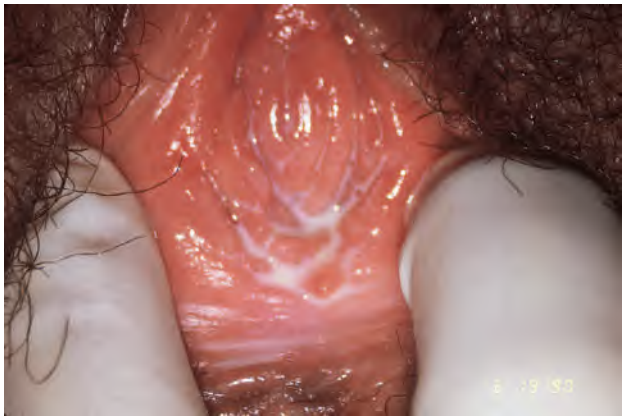

FIG. 108.5 Trichomoniasis. There are purulent secretions and mucosal erythema.

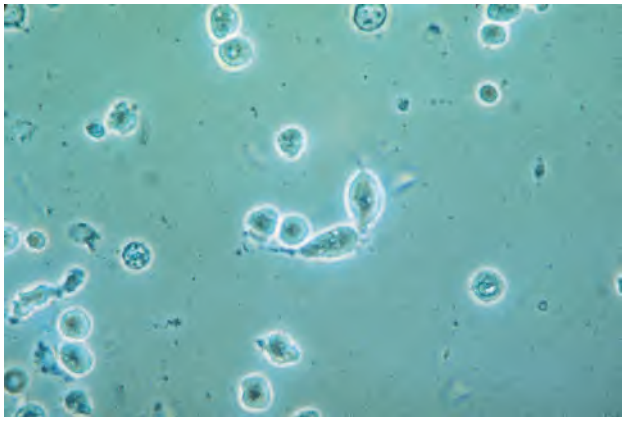

FIG. 108.6 Trichomoniasis suspension. Suspension of vaginal secretions in 0.9% sodium chloride. There are leukocytes and flagellated trichomonads.

Therapy

Metronidazole and tinidazole are the only effective agents that are approved by the FDA for the treatment of trichomoniasis. A single 2-g oral dose of metronidazole or tinidazole can be prescribed. Alternatively, 500 mg of oral metronidazole can be given twice daily for 7 days. Single-dose therapy may be less effective in HIV-infected women, and a recent meta-analysis suggested the same may be true in HIV-uninfected women. A single-dose regimen, if administered under direct observation in the office or clinic, has the obvious advantage of 100% compliance. Because trichomoniasis is almost always sexually transmitted, treatment with metronidazole of all recent sexual partners, regardless of their symptoms, is an integral part of management.[24]

The aforementioned regimens containing metronidazole or tinidazole eliminate trichomonads in well over 90% of instances. Tinidazole is considerably more expensive than metronidazole. If this treatment fails (Table 108.8) the diagnosis should be reconfirmed with a wet preparation or culture. In addition, treatment of all current sexual partners should be ensured. Initial re-treatment should be with oral metronidazole, 500 mg twice daily for 7 days. If this regimen is not successful, oral metronidazole or tinidazole in a single daily dose of 2.0 g can be prescribed for 7 days.[24] If the latter regimens fail, the patient can be assumed to have clinically significant resistance, and consultation with an expert in the management of trichomoniasis should be sought. Susceptibility testing, available through the Centers for Disease Control and Prevention (CDC), should be performed.[25] Metronidazole resistance may occur in 4% to 10% of cases of vaginal trichomoniasis, and tinidazole resistance may occur in 1%.[25,26] Intravenous regimens of metronidazole have been prescribed in instances of trichomoniasis drug resistance.[27] For patients who cannot tolerate metronidazole at recommended dosages and for those who do not respond to it, tinidazole has better in vitro efficacy,[28] is better tolerated than metronidazole, and has cured most patients with metronidazole-resistant trichomoniasis.[29] Alternative regimens in nitroimidazole-resistant infections include high-dose tinidazole 2 to 3 g for 14 days, often in combination with intravaginal tinidazole.

For patients with trichomoniasis who are unresponsive to metronidazole and tinidazole, there are few therapeutic options of proven value. Nonoxynol-9 is active against *T. vaginalis* in vitro and was reported to be effective in 1 patient.[30] However, in a subsequent study, nonoxynol-9 was effective in only 3 of 17 patients.[31] Furazolidone is highly active in vitro against metronidazole-sensitive and metronidazole-resistant isolates of *T. vaginalis*[32] and was effective when given vaginally in a study conducted years ago.[33] In one study[34] vaginal acidification with boric acid was effective. In general, however, topical treatments have been disappointing,[16] presumably because of reservoirs of infection in periurethral glands and other areas that are not adequately sterilized by intravaginal medications. Specifically, topical preparations containing metronidazole (e.g., 0.75% metronidazole gel) have been ineffective in unselected patients with trichomoniasis[35] and are of no use in patients with metronidazole resistance, except as a possible adjunct to oral treatment. Repeat testing should be performed in 3 months as recommended by current CDC guidelines; the rationale of retesting is that reinfection rates are as high as 17%.[36]

T. vaginalis organisms have been shown to be estrogen dependent in vitro[37] and in vivo.[38] In one report discontinuation of estrogen replacement treatment in a postmenopausal woman was associated with resolution of vaginal trichomoniasis.[39] These data suggest that hormonal manipulation should be studied in the management of trichomoniasis that is unresponsive to metronidazole and tinidazole and for women who cannot tolerate these drugs.

TABLE 108.8 Management of Trichomoniasis Treatment Failures

Reconfirm diagnosis
Wet preparation
Culture
Confirm that all current sexual partners have been treated
Re-treat with oral metronidazole or tinidazole
Consultation with an expert
Susceptibility testing

Minor adverse reactions to metronidazole, primarily nausea and a metallic taste, are common, but most patients can tolerate the usual dosage schedules. Metronidazole allergy is unusual. In such instances desensitization has been useful.[40]

About half of women with HIV infection are also infected with *T. vaginalis*.[41] Treatment of trichomoniasis with 500 mg of metronidazole twice daily for 7 days decreases the viral load of HIV in vaginal fluid,[42] an observation concordant with the results of studies that show an association of trichomoniasis with HIV acquisition.[43]

Pregnancy

Trichomoniasis in pregnancy has been the subject of considerable interest. An association between trichomoniasis and premature rupture of the membranes was reported in 1984.[44] Cotch and colleagues,[45] using data from the Vaginal Infections and Prematurity Study, reported in 1997 on the prospective evaluation of 13,816 pregnant women. They found that trichomoniasis was independently associated with a 30% greater likelihood of preterm delivery and low birth weight, and a 40% greater likelihood of having a preterm infant of low birth weight. In a more recent study treatment of trichomoniasis in asymptomatic pregnant women with metronidazole did not prevent preterm delivery.[46] Metronidazole has traditionally been avoided during pregnancy because of largely theoretical concerns about mutagenicity and oncogenicity. However, studies and meta-analyses have not demonstrated a consistent association between metronidazole use during pregnancy and teratogenic or mutagenic effects in infants.[47–49] Therefore pregnant women who have symptomatic trichomoniasis may be treated with 2 g of metronidazole.[24] Tinidazole has not been well evaluated in pregnant women. In lactating women, breastfeeding should be stopped during treatment and for 12 to 24 hours after completion of treatment with metronidazole, and for 3 days after completion of treatment with tinidazole.[24]

VULVOVAGINAL CANDIDIASIS

VVC is the second most common cause of vaginitis after BV.

Etiology and Pathogenesis

Candida albicans and other species of *Candida* can be part of the vaginal microbiota of asymptomatic women. About 30% of unselected women are colonized. In one study of unselected women[15] two-thirds of colonized women and only 22% of uncolonized women reported symptoms, primarily vulvovaginal itching and irritation. These data suggest that colonization with *Candida* spp. usually produces symptoms, albeit mild symptoms that do not prompt the patient to seek medical attention.

C. albicans can be isolated from 80% to 90% of patients with VVC, and other yeasts account for up to 20% of cases.[50] *Candida tropicalis* is isolated from 1% to 5% and may be associated with a higher rate of recurrence after standard treatments.[51,52] *Candida* (formerly *Torulopsis*) *glabrata* accounts for about 10% of vaginal yeast isolates.[50,51,53–55] Symptomatic vaginitis caused by this organism is associated with less intense itching and dyspareunia[53] than that caused by other *Candida* spp., but the organism may be harder to eradicate with standard therapies.[51,55] The relative incidence of vaginitis caused by fungi other than *C. albicans* appears to be increasing. Non-*albicans* infections are associated with recurrent disease (accounting for 21% of recurrent vs. 12% of initial infections) and with HIV infection (22% of infections in HIV-positive women vs. 12% in HIV-negative women), especially in HIV-infected women who receive prophylaxis with imidazoles or triazoles.[51] It is believed that the widespread use of topical antifungal agents, especially in short courses, may contribute to selection for non-*albicans* yeasts, which are less susceptible to these agents than is *C. albicans*. Cases of vaginitis caused by *Saccharomyces cerevisiae* have been reported and may be associated with baking.[56,57]

Some workers have estimated that 75% of adult women will suffer at least one episode of VVC during their lifetime.[58] Inhibition of normal bacterial microbiota by antibiotics favors the growth of yeasts,[58,59] although symptomatic cases are seen after the use of antimicrobial agents that do not suppress lactobacilli.[60] VVC sometimes occurs after antimicrobial treatment of trichomoniasis or BV.

Growth of yeasts is apparently favored by high estrogen levels, although such levels also promote the growth of lactobacilli.[61–63] The

prevalence of vaginal carriage of *Candida* is higher among users of oral contraceptives than among women using other methods of birth control.[59,63] The mechanism of this estrogenic predisposition is unclear.

VVC is associated with poorly controlled diabetes mellitus, and tight glycemic control decreases the frequency of symptomatic infection.[64] However, testing for diabetes in women with recurrent VVC is not cost effective because the yield is low.[59]

It has been suggested that tight, insulating clothing predisposes to VVC by increasing vulvar warmth and moisture. In prospective studies a higher prevalence of candidal carriage and higher concentrations of organisms were found in women who wore tight rather than loose clothing.[65–67] Impairment of phagocytic cells or of cell-mediated immunity (e.g., transplantation, chemotherapy) also predisposes to VVC. Some authorities believe that women with HIV infection develop VVC more often than HIV-negative women do, especially if they have low CD4 T-cell counts.[68,69]

The contribution of sexual transmission is poorly defined. VVC increases in incidence with the onset of sexual activity,[70–72] but the incidence is also increased by the use of oral contraceptives,[59,63] the contraceptive sponge, or the intrauterine device,[67] any of which might coincide with sexual activity. Having multiple sexual partners is not associated with a higher incidence of *Candida* infection. Most women who present with VVC have no predisposing illnesses or medications.

The mechanism by which *Candida* produces disease is not well defined. Although it is postulated that differences in virulence must exist,[59] strains isolated from symptomatic women are not demonstrably different from isolates from asymptomatic carriers.[73] Filamentous forms (hyphae and pseudohyphae) are associated with active disease.[74] Pseudohyphae have been observed to penetrate vaginal epithelial cells,[75] and they are more adherent to cells than are budding yeasts (blastospores).[76] Adherence appears to be an important pathogenic feature of *Candida* spp.,[77] and sublethal concentrations of antifungal agents may ameliorate disease by reducing adherence.[78] This suggested that *Candida* organisms entered the vagina via migration from the rectum across perianal area.[79]

The severity of symptoms in VVC is not directly related to the number of yeast cells present. Indeed, very small numbers of yeasts may be present in vaginal material recovered from highly symptomatic women.[59]

Clinical Manifestations

Patients with candidal vulvovaginitis generally complain of perivaginal pruritus, often with little or no discharge (Table 108.9). Dysuria is occasionally noted and is likely to be perceived as vulvar rather than urethral. The labia may be pale or erythematous. Shallow, radial, linear ulcerations (Fig. 108.7), especially on the posterior portion of the introitus, are common. Excoriations caused by scratching are often present (Fig. 108.8). Tiny papules or papulopustules, called satellite lesions, just beyond the main area of erythema are helpful diagnostically. The vaginal walls may be erythematous. Candidal discharge is classically thick cottage cheeselike and adherent, which presents a strong clue as to the cause of the infection (Fig. 108.9). However, discharge may be thin and loose, resembling that of other vaginitides.

Diagnosis

Vaginal pH is usually normal. There is no odor when the vaginal secretions are mixed with 10% KOH. Microscopic examination of vaginal material in saline or in 10% KOH may disclose budding yeasts or mycelia (Fig. 108.10). In the symptomatic patient with a diagnostic microscopic examination, fungal cultures are not needed. Microscopic examination of vaginal secretions is incompletely sensitive and is negative in 50% of culture-confirmed VVC.[80] In accordance, cultures may be helpful to secure the diagnosis in a patient who has a compatible clinical presentation and a negative microscopic examination. It is usually expedient to treat such a patient with antifungal agents while awaiting culture results. Cultures are also useful if empirical treatment produces no response. DNA probe testing can identify the presence of yeast, although not its role in causing disease. Polymerase chain reaction (PCR) testing for yeast is not FDA cleared. Culture remains the gold standard for diagnosis.

TABLE 108.9 Symptoms of Vulvovaginal Candidiasis

Vulvar itching
Vulvar irritation
Dysuria
Dyspareunia
Abnormal vaginal discharge

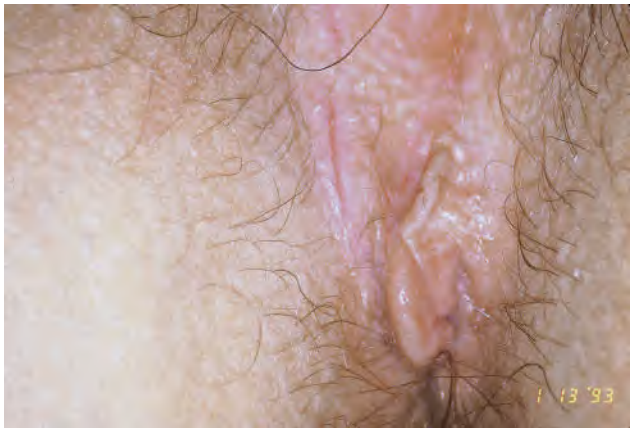

FIG. 108.7 Vulvovaginal candidiasis. There is a linear ulcer of the perineal skin.

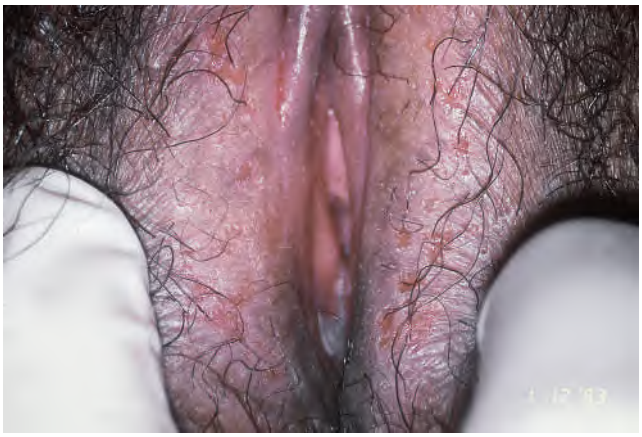

FIG. 108.8 Vulvovaginal candidiasis. There are excoriations of the skin of the labia majora due to scratching.

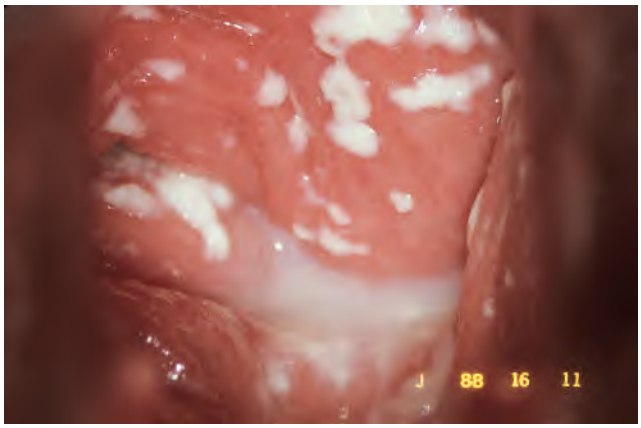

FIG. 108.9 Vulvovaginal candidiasis. There are adherent white patches with surrounding erythema on the cervical mucosa.

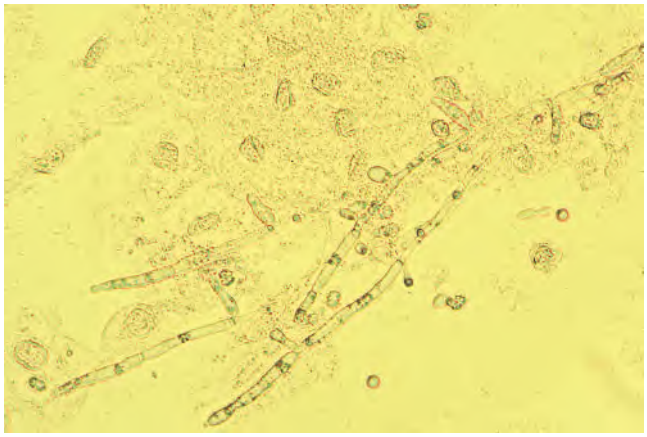

FIG. 108.10 Vulvovaginal candidiasis. Suspension of vaginal secretions in 0.9% sodium chloride. Mycelia can be seen.

TABLE 108.10 Classification of Patients With Vulvovaginal Candidiasis

Uncomplicated Infection
Sporadic or infrequent
Mild-to-moderate severity
Likely to be caused by *Candida albicans*
Patient is not immunocompromised
Complicated Infection
Recurrent infection (four or more episodes per year)
Severe infection
Caused by non-*albicans* species of *Candida*
Uncontrolled diabetes, debilitation, immunosuppression, or pregnancy

TABLE 108.11 Treatment of Vulvovaginal Candidiasis

Uncomplicated Infection
Any available topical agent, short course
Fluconazole, 150 mg as a single oral dose
Complicated Infection
Culture confirmation mandatory
Antifungal susceptibility testing may be helpful
Treatment for 10–14 days with vaginal or oral agents
Alternative topical agents
Boric acid
Consider treatment of partners
Long-term suppressive treatment for frequently recurrent disease

Therapy

The treatment of VVC is best approached by classifying the patient as having either uncomplicated or complicated infection (Tables 108.10 and 108.11).[24]

Uncomplicated VVC is a sporadic infection with *C. albicans* of mild-to-moderate severity in a woman without a history of recent candidiasis and without underlying illness, such as HIV infection or diabetes mellitus. Most patients have uncomplicated disease, and most cases respond to treatment with short courses of vaginal or oral antifungal agents. Effective agents include vaginal preparations containing nystatin, miconazole, clotrimazole, butoconazole, terconazole, and tioconazole. All except nystatin- and terconazole-containing products are available without a prescription. Self-diagnosis and self-medication with OTC antifungal agents should be limited to women who have previously had documented VVC and are experiencing a recurrence of similar symptoms; self-diagnosis in other situations is often erroneous.[81] Failure to respond to self-medication should trigger a visit to a physician. In uncomplicated disease there does not appear to be any difference in efficiency related to dosage form (vaginal tablets, suppositories, ointments, creams) or to length of treatment (1, 3, 7, or 14 days). Oral fluconazole in a single 150-mg dose is as effective as the aforementioned vaginal medications in the treatment of uncomplicated VVC[82] and has been approved by the FDA for this indication. Oral fluconazole may be less expensive than some topical preparations and is preferred over topical treatments by many women. In this dosage the side effects are few[82] and systemic toxicity is unlikely. Other oral antifungal agents, such as ketoconazole, itraconazole, and voriconazole, are effective.

Complicated VVC occurs in patients with underlying conditions that compromise the immune response, such as diabetes, HIV disease, malignancy, or treatment with immunosuppressive agents. Patients who are pregnant or who have severe disease and patients with frequent recurrences (four or more episodes during the past year) should also be considered to have complicated disease, as should women infected with species other than *C. albicans.*

Management of complicated disease should begin with a vaginal culture to confirm the diagnosis and to determine the species of any isolated yeast. More than half of patients referred because of *chronic fungal vaginitis* have negative yeast cultures and a noninfectious explanation for their symptoms.[83] It is important that these misdiagnosed patients be culled at the outset so that needless and predictably futile antifungal treatment can be avoided and attention directed to establishing an accurate diagnosis. Speciation is important for those patients who do have candidiasis because infections caused by species of *Candida* other than *C. albicans* are often more difficult to treat.[84]

Complicated VVC responds poorly to short courses of treatment with oral fluconazole[85] or topical preparations. Treatment for 7 to 14 days or longer of topical therapies or oral fluconazole every other or third day for three doses is usually required. For patients with recurrent infections, chronic suppressive treatment with an oral antifungal agent may be useful in preventing recurrences once the current infection has responded. In 2004 150 mg of fluconazole per week was evaluated.[86] Recurrences are infrequent during chronic suppressive treatment, which is continued for at least 6 months. Once suppressive treatment is discontinued, relapse occurs in about half of the patients, necessitating continued chronic suppression.

Pregnant women should be treated with topical agents for at least 7 days. Oral azole antifungal agents should not be used during pregnancy because its impact on miscarriage risk is unclear, and high doses appear to increase the risk of birth defects.

Because a significant minority of healthy women are colonized with *Candida* spp., treatment is not indicated for asymptomatic women who have positive vaginal cultures.

Resistance to antifungal agents appears to be increasing. The availability of OTC antifungal agents and the widespread use of oral agents (e.g., ketoconazole, fluconazole, itraconazole), especially in patients with HIV disease, are possible explanations. In any event, an increasing number of cases do not respond to the usual topical and oral agents. Species other than *C. albicans,* such as *Candida krusei*[87] and *C. glabrata,* are more likely to be resistant, but nonresponsive *C. albicans* isolates are also beginning to appear.[88,89]

Fungal susceptibility testing is neither widely available nor easy to interpret. The National Commission for Clinical Laboratory Standards has published guidelines.[90]

Laboratories should offer testing using these guidelines. In vitro resistance predicts treatment failure, whereas in vitro susceptibility to a given agent is more difficult to interpret.

For VVC that does not respond to the available topical and oral agents, or is caused by non–*albicans Candida* (i.e., *C. glabrata*) intravaginal boric acid has been used with success.[91] Boric acid powder (600 mg) is placed into size 0 gelatin capsules and administered vaginally for 14 days. Ninety percent cure has been achieved with intravaginal flucytosine cream or amphotericin B cream. It should be noted that boric acid capsules, amphotericin B cream, and flucytosine cream are not available commercially in the United States.

Treatment of sexual partners has no role in the treatment of sporadic uncomplicated infections, but it may be worth considering for patients who have recurrent infections. Sequential isolates from such patients tend to be identical,[92] suggesting endogenous reactivation or exogenous reinfection from the same partner. Because the responsible organism

can often be recovered from male sexual partners,[93] they cannot be ruled out as a possible source of reinfection.

An immunologic hyperreactivity reaction has been suggested as the mechanism of symptomatic and recurrent vulvovaginitis. Activation of a complex immune reaction that releases different kinds of interleukin (IL)—IL-22, IL-10, IL-17, IL-1, and IL-18—activates T cells (Th1, Th17) and has been attributed to anti-*Candida* protection. The same mechanism, if inappropriately or excessively stimulated, causes damage through stimulation of an overwhelming inflammation that impairs the anti-*Candida* defense.[94]

The advance in the knowledge of host immune responses to *C. albicans* has provided a solid background for the generation of anti-*Candida* vaccines; some are under clinical investigations, with recurrent VVC being the main indication.[95]

Use of probiotics to treat and prevent VVC is a long-standing tradition. In the absence of controlled studies the use of probiotics is not part of recommended regimens.

BACTERIAL VAGINOSIS

Many women who present to their physicians with vaginal symptoms have a specific condition, first described by Gardner and Dukes[96] in 1955, that is now referred to as BV.[97,98] Perivaginal irritation is considerably milder than in trichomoniasis or candidiasis. Dysuria and dyspareunia are correspondingly rare. Affected women are usually sexually active and often complain of vaginal odor, which frequently is described as "fishy." About 90% of patients also notice a mild-to-moderate discharge. Abdominal discomfort is occasionally present, but it is usually mild and should prompt evaluation for coincident infections such as salpingitis.

Discharge is often present at the introitus and visible on the labia minora. The labia and vulva are not erythematous or edematous. On speculum examination the vaginal walls appear uninflamed. The vagina usually contains a grayish, thin, homogeneous discharge. A pungent odor may be noted by the examiner.

The endocervix is unaffected by the process, and any cervical discharge should be physiologic. The presence of a purulent cervical discharge may result from coincident gonococcal or chlamydial infection.[99] Abnormalities on bimanual examination are unusual in uncomplicated BV and should prompt a search for other pathologic processes. There is an increased risk for endometritis and salpingitis among women with BV.[100–102]

Other vaginal infections may resemble BV; an accurate differential diagnosis depends on laboratory examination. The pH of vaginal fluid is elevated to greater than 4.6 in about 90% of women with BV.[96,103,104] A vaginal pH of 5 or higher strongly suggests BV.[105] A whiff test is positive.[103,106]

A wet mount of the vaginal fluid from patients with BV usually reveals clue cells, which are vaginal epithelial cells studded with tiny coccobacilli. These organisms are best appreciated at the edges of the cell and may be dense enough to partially obscure the nucleus. Not all cells in the specimen are clue cells, but some clue cells are seen in more than 90% of patients with BV.[107,108] A finding of increased numbers of PMNs in a patient with BV suggests the presence of a coexisting process, notably cervicitis.[99]

Culture for *Gardnerella vaginalis* can be accomplished on a variety of media (see Chapter 236), and DNA probe technology has also been used for its identification in vaginal specimens. The organism can be isolated from virtually all women with BV,[98,106] but it is also recovered from at least 50% of asymptomatic women.[98] Therefore the presence of *G. vaginalis* does not prove that a patient has BV or suggest a need for treatment. A positive culture or nonculture test for *G. vaginalis* should not be considered diagnostic of BV unless other objective evidence of BV (elevated pH, odor with 10% KOH, clue cells) is present.

Epidemiology

In the United States, according to the National Health and Examination Survey, the prevalence of BV is 29% in women age 14 to 49 years and 50% in African-American women.[109]

Bacterial vaginosis was initially described in sexually active women, and it is common in populations with a high prevalence of STDs. The precise contribution of heterosexual transmission to the overall epidemiology of the condition remains controversial. However, a recent meta-analysis[110] found a significant positive association between BV and new or multiple sexual partners and a significant negative association between BV and condom usage. The prevalence is appreciable in lesbians, among whom other STDs are relatively uncommon. In one study women who identified as lesbians had a 2.5-fold increased likelihood of BV compared with heterosexual women. Lesbian couples are mostly concordant with regard to vaginal microbiota (normal or BV), suggesting that BV is sexually transmitted in this setting.[111,112]

Pathophysiology

Microscopic examination of vaginal discharge in BV characteristically reveals a predominant microbiota of coccobacilli. On the basis of this morphology the organism most closely associated with BV was originally called *Haemophilus vaginalis*.[96] It has now been given its own genus and is called *G. vaginalis* in recognition of Gardner's initial observations (see Chapter 236). Several studies suggest a less-than-straightforward relationship between *G. vaginalis* and BV. Although Gardner regularly produced BV by inoculating fresh vaginal discharge from patients with BV into the vaginas of healthy volunteers, inoculation of a pure culture of *G. vaginalis* was far less likely to produce disease.[96] In addition, *G. vaginalis* can be isolated from about 50% of asymptomatic women.[113] Finally, the in vitro sensitivity of *G. vaginalis* to antimicrobial agents does not match the effectiveness of these agents in clinical disease. Metronidazole is highly effective therapy for BV despite the fact that *G. vaginalis* is relatively resistant to the drug in vitro.[103]

Dysbiosis

Although the pathogenesis of BV remains unclear, alternatively, it represents a dysbiosis, an imbalance of the vaginal microbiota rather than an infection. BV is characterized by a shift from the predominance of lactobacilli in the vaginal microbiota to a higher concentration of other organisms.[114]

One explanation for all of these observations is that *G. vaginalis* is not the single cause of BV. BV is actually a synergistic infection involving not only *G. vaginalis* but also other microorganisms. The total diversity of culturable vaginal organisms is dramatically increased in women with BV. Organisms usually found in the intestinal tract include *Prevotella, Megasphaera,* Coriobacteriaceae, Lachnospiraceae, *Sneathia*, *Porphyromonas, Bacteroides* spp., and *Peptostreptococcus* spp., as well as BV-associated bacteria (BVAB)-1, BVAB-2, and BVAB-3.[115,116]

Most cases of BV are also associated with motile, curved anaerobic rods that are gram negative or gram variable. These organisms have been classified into the genus *Mobiluncus*.[117] Similarly, *Atopobium vaginae* is found in high titers in the vaginal fluids of most women who have BV.[118] The precise pathogenic role of these organisms remains to be elucidated. *Mycoplasma hominis* and *Ureaplasma urealyticum* can be isolated from the vagina in many women with BV. Their role as etiologic agents of BV has not been established.

Hydrogen Peroxide Production

Hydrogen peroxide (H_2O_2)–producing lactobacilli dominate the normal vaginal microbiota[2] and appear to protect against exogenous infection. Some workers believe that an undefined change in the vaginal milieu permits the replacement of protective H_2O_2-producing lactobacilli with *G. vaginalis* and other anaerobic microorganisms as mentioned earlier.

Biofilm Formation

Evidence suggest that *G. vaginalis* is the inciting pathogen in the pathogenesis of BV. Although the other anaerobic organisms contribute to BV symptoms, *G. vaginalis* play a role in the process of biofilm development. It has the ability to adhere to host receptor sites on vaginal epithelial cells and induce the production of cytotoxic substances specific to host cells and biofilm formation.[119]

Risk Factors

Some investigators have linked douching and smoking to BV.[120–122]

Women who have BV are at increased risk for the development of infection with HSV type 2,[123] *N. gonorrhoeae,* and *C. trachomatis*.[4]

BV has been associated with an increased risk for HIV infection.[124] In one study BV was associated with HIV-1 RNA expression in the genital tract of infected women,[125] consistent with the hypothesis that BV predisposes to the acquisition of HIV-1 infection.

Diagnosis

The patient is most likely to complain of odor and of the discharge, which tends to be gray and homogeneous (Fig. 108.11). The odor is best described as "fishy" and is caused by amines such as methylamine. These amines volatilize at increased pH, which explains the propensity of the patient to notice the odor when her secretions are more alkaline (e.g., during menses, after intercourse). Vulvovaginal irritation is not usually a prominent symptom, hence the use of the term *vaginosis* rather than *vaginitis*. Table 108.12 details the symptoms usually associated with BV.

Vaginal pH is typically elevated to greater than 4.6. Odor is produced when vaginal secretions are mixed with 10% KOH. Microscopic examination of vaginal secretions suspended in 0.9% sodium chloride (NaCl) reveals few leukocytes and many small bacilli. The bacilli tend to coat vaginal epithelial cells, the so-called clue cells (Fig. 108.12), so named by Herman Gardner because they provided a *clue* to the diagnosis of this condition.[96]

Criteria for the diagnosis of BV are listed in Table 108.13. Amsel and colleagues[106] suggested that at least three of the four listed criteria (homogeneous discharge, positive whiff test, pH greater than 4.6, clue cells) should be present for the diagnosis of BV to be made. Clinicians' descriptions of the discharge tend to be poorly reproducible, and some workers prefer to require that all three of the somewhat more objective criteria be present. Criteria have been developed by Nugent and colleagues[126] for the diagnosis of BV with use of the vaginal Gram stain. This is an objective method of diagnosis that compares well[127] with the criteria of Amsel. Other tests have acceptable performance characteristics compared with Gram stain include Affirm VPIII (BD Life Sciences, Franklin Lake, NJ), a DNA hybridization probe test for high concentration of *G. vaginalis* and OSOM BVBlue test (Sekisui Diagnostics, Lexington, MA), which detects vaginal fluid sialidase activity. These tests can be used when microscopy is not available.

The proline aminopeptidase card test is not recommended due to low sensitivity. PCR assay directed at a variety of organisms associated with BV has been used in research setting. More data are needed for evaluation of its clinical utility.[116,128]

Therapy

Therapy is indicated in symptomatic women to relieve their symptoms and prevent acquisition of other STDs, such as chlamydia, gonorrhea, HIV, HSV-2, and trichomoniasis. The primary regimen for the treatment of BV is oral metronidazole, 500 mg twice a day for 7 days. A single 2.0-g dose of metronidazole, such as is used to treat trichomoniasis, is less effective and is not recommended.[129] Vaginal preparations containing 0.75% metronidazole gel[130] or 2% clindamycin cream,[131] or ovules containing 100 mg of clindamycin,[132] are effective and have few systemic side effects. They are, however, more expensive than generic oral metronidazole. Secnidazole is a nitroimidazole approved by the FDA in September 2017 for women with BV as single 2-g oral dose. Oral clindamycin also is effective, but it is not widely prescribed for this indication. Alternative regimens, such as oral tinidazole 1 g once daily for 5 days or 2 g daily for 2 days, have been shown to be effective.[133] The FDA has also cleared metronidazole administered as 750-mg extended-release tablets once daily for 7 days and a single dose of clindamycin vaginal cream; however, data on the performance of this alternative regimen are limited.[24]

Treatment failures occur fairly commonly,[134] presumably because a normal *Lactobacillus*-dominated microbiota fails to become reestablished after the anaerobes and other components of the BV microbiota have been reduced in number with use of antimicrobial agents. Recent studies have shown that persistence of *G. vaginalis* in biofilms on the vaginal wall may be associated with treatment failure.[135,136]

For patients with multiple recurrences after completion of a recommended regimen, 0.75% Metrogel twice a week for 4 to 6 months or monthly oral metronidazole 2 g with fluconazole 150 mg have been shown to reduce recurrence rates.[137,138]

For patients who have BV that is unresponsive to the currently available antimicrobial agents, intravaginal boric acid, 600 mg at bedtime, provides symptomatic relief. Once the symptoms have been controlled, the dosing interval can be increased. Some patients remain free of symptoms using boric acid capsules once or twice a week.

Probiotics have been used alone or with antibiotics for therapy and prevention of recurrence of BV. No studies support the addition of any available *Lactobacillus* or probiotic formulation as adjunctive or replacement therapy in women with BV.[139,140]

Postoperative infections occur more often in women undergoing gynecologic surgery if they have BV than if they have normal microbiota.[5] In one study[141] women who had BV and who underwent total abdominal hysterectomy were randomly assigned to receive metronidazole or no

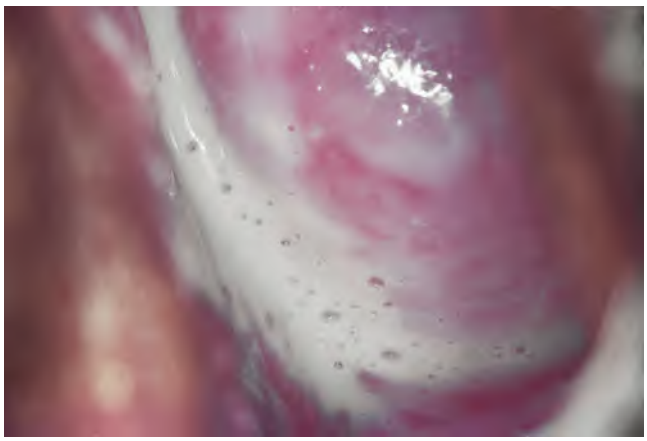

FIG. 108.11 Bacterial vaginosis. The gray, homogeneous discharge that coats the tissues is characteristic.

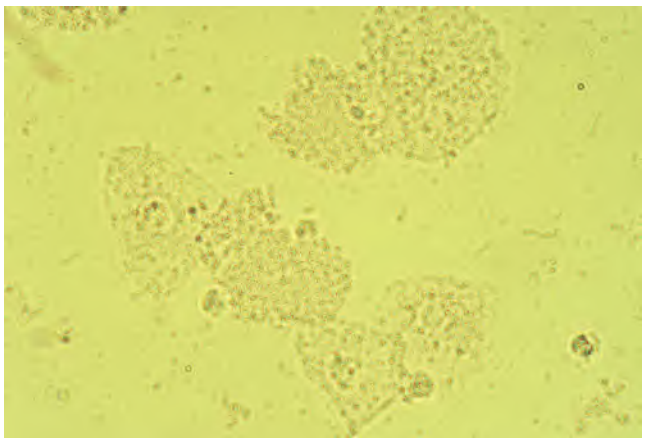

FIG. 108.12 Bacterial vaginosis. Suspension of vaginal material in 0.9% sodium chloride. Many bacteria are attached to the vaginal epithelial cells (clue cells).

TABLE 108.12 Symptoms Associated With Bacterial Vaginosis

Homogeneous vaginal discharge
Fishy vaginal odor during menstruation or after intercourse
Minimal itching or irritation

TABLE 108.13 Criteria for the Diagnosis of Bacterial Vaginosis

Homogeneous vaginal discharge
Vaginal pH >4.6
Positive whiff test with 10% potassium hydroxide
Clue cells

treatment. Vaginal cuff infections occurred in none of the treated women but in 27% of the untreated women ($P < .01$). Treatment studies have demonstrated that treatment of BV before induced abortion reduces the risk for subsequent pelvic inflammatory disease.[142] Therefore it would appear prudent to screen and treat women who have BV before performing induced abortion or hysterectomy. This logic could be extended to women undergoing other invasive gynecologic procedures, although there have been no studies in those areas.

Pregnancy

Pregnant women who have symptomatic BV should be treated.[24] BV during pregnancy is associated with adverse pregnancy outcomes, including premature membrane rupture, early labor, preterm birth, and postpartum endometritis.[143–145] Treatment of pregnant women who have BV and who previously delivered a premature infant reduced the risk for preterm delivery.[146–148] In accordance, pregnant women who are at high risk for preterm delivery should be screened for BV, regardless of symptoms and, if affected, treated with oral metronidazole or oral clindamycin.[149] Topical agents do not appear to be as effective as oral agents, and the use of clindamycin cream has been associated with adverse events such as prematurity and neonatal infections.[150,151]

Treatment of pregnant women who have asymptomatic BV and who are at low risk for premature delivery is controversial.[152–154] An analysis of 21 clinical trials involving 7847 women showed that antibiotic treatment of BV during pregnancy eradicated bacterial vaginosis, but the overall risk for preterm birth was not significantly reduced.[155]

BV can be nonsymptomatic. Women without symptoms are not usually treated, although the approach to such patients may change as more is learned about the implications of having abnormal vaginal secretions. Some women with nonsymptomatic BV who receive treatment retrospectively notice improvement in vaginal discharge and odor. Although BV is not considered a classic STD, studies support the notion that sexual activity is a risk factor. Women who have never been sexually active are rarely affected.[156]

Several studies have failed to show that treatment of male sexual partners improves the outcome of women treated for BV, although these studies were not of high quality.[157] Some clinicians treat sexual partners of women who have recurrent BV or BV that is poorly responsive to treatment with metronidazole or clindamycin. Although such an approach appears to be reasonable, there is no supporting scientific evidence.

Bradshaw and colleagues[158] studied 450 women who were treated for bacterial vaginosis. Recurrent BV was associated with sexual contact with their pretreatment sexual partner and inconsistent condom use. Recurrence was halved in association with the use of estrogen-containing contraceptives.[158] These data provide further support for the importance of sexual transmission in the epidemiology of bacterial vaginosis and suggest that change in the vaginal environment produced by estrogen may facilitate restoration of normal microbiota after treatment of bacterial vaginosis.[159]

DESQUAMATIVE INFLAMMATORY VAGINITIS

Etiology and Pathogenesis

DIV is an unusual condition of unknown cause. It mimics estrogen-deficiency vaginitis and trichomoniasis but usually occurs in women of reproductive age who have normal hormonal function and no evidence of any sexually transmitted conditions.

Some investigators believe it is an inflammatory vaginitis of noninfectious etiology; others consider it as representing a defect in vaginal microbiota and have named it "aerobic vaginitis."[160,161] In a few patients DIV appears to be a local manifestation of a systemic illness, such as systemic lupus erythematosus. Patients with DIV may also have erosive lichen planus involving oral or genital mucous membranes. Some investigators[162] have suggested that DIV is always part of the lichen planus complex. The paucity of occasions when these two enigmatic conditions coexist does not support this conclusion.[163]

Diagnosis

The patient reports purulent vaginal discharge and varying degrees of vulvar irritation, dysuria, and dyspareunia (Table 108.14). There is often a history of multiple unsuccessful treatments with a variety of topical and oral antimicrobial agents. Because the disease is most often confused with trichomoniasis, frequently in patients in whom a sexually transmitted condition is highly unlikely, many patients carry the diagnosis of resistant trichomoniasis and have received several courses of metronidazole in various dosage forms and dosages.

The mucosa of the vestibule, vagina, and cervix may show diffuse (Fig. 108.13) or segmental involvement, usually in the proximal vagina. There may be superficial erosions of the mucosa, which are characteristic of this condition (Fig. 108.14).

The vaginal pH is often elevated to greater than 4.6. There is no odor when the vaginal secretions are mixed with 10% KOH. The saline

TABLE 108.14 Characteristics of Desquamative Inflammatory Vaginitis

Symptoms
Purulent discharge
Vulvar discomfort
Dyspareunia
Findings
Mucosal erythema
Purulent secretions
Parabasal cells
Treatment
Clindamycin 2% vaginal cream
Boric acid
Topical corticosteroids

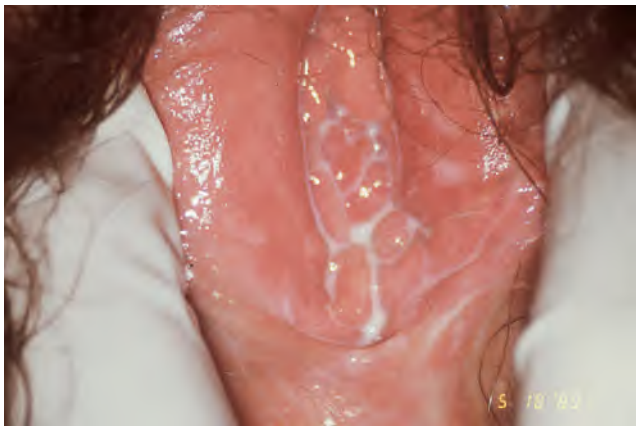

FIG. 108.13 Desquamative inflammatory vaginitis. Diffuse mucosal erythema and a purulent vaginal discharge are evident.

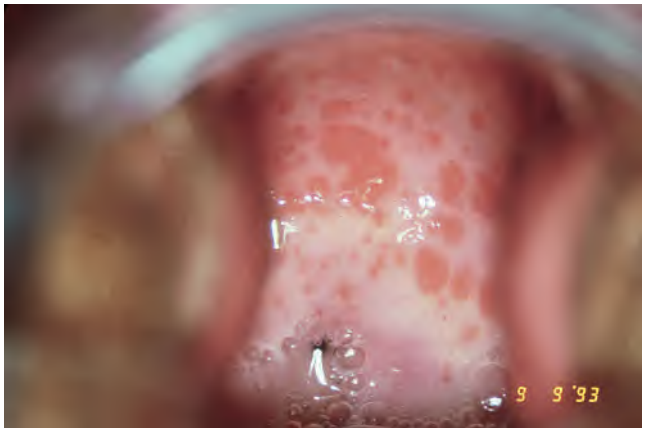

FIG. 108.14 Desquamative inflammatory vaginitis. Superficial mucosal erosions can be seen.

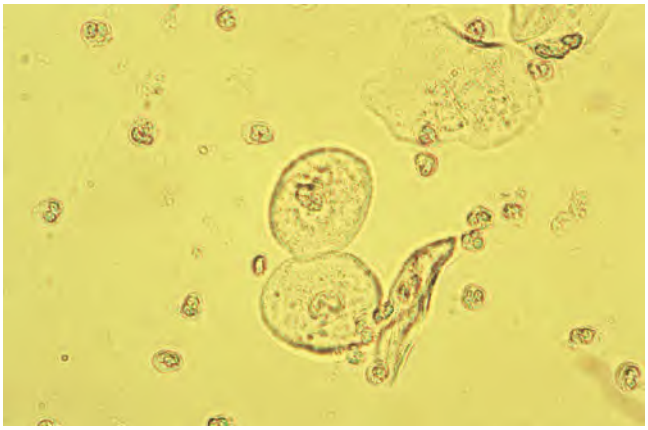

FIG. 108.15 Desquamative inflammatory vaginitis. The vaginal wet preparation contains many leukocytes and parabasal cells.

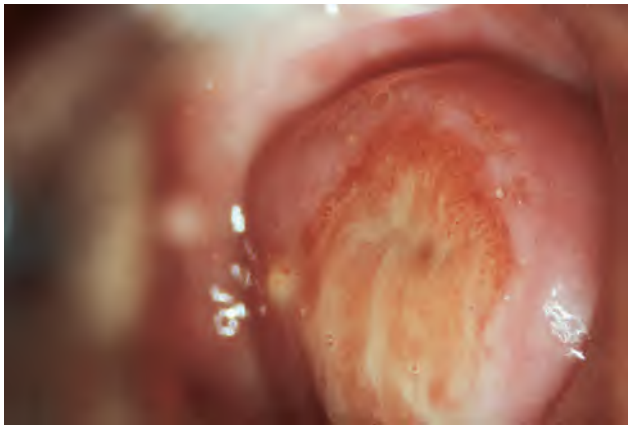

FIG. 108.16 Noninfectious purulent ectocervicitis. Purulent secretions can be seen to emanate from the ectropion.

TABLE 108.15 Cervicitis

Endocervicitis
Sexually transmitted *Neisseria gonorrhoeae, Mycoplasma genitalium, Chlamydia trachomatis* Associated urethritis, endometritis, or salpingitis may be present
Ectocervicitis
Noninfectious Inflammation in an ectropion Not associated with urethritis, endometritis, or salpingitis

wet preparation contains many leukocytes. Most of the vaginal epithelial cells are immature parabasal cells (Fig. 108.15).

Therapy

Topical corticosteroids and topical boric acid provide symptomatic relief and normalize the appearance of the mucous membranes and vaginal secretions. Relapse is predictable after these agents are discontinued. By far the most effective treatment for this condition is 2% clindamycin vaginal cream: 5 g of the cream, containing 100 mg of clindamycin, is inserted into the vagina at bedtime for 4 weeks. Most patients have a prolonged remission after this course of treatment. A few patients require a second 4-week course of treatment to induce a remission, but at least 90% of patients with DIV experience a complete remission in association with treatment with topical clindamycin.[164]

Once remission has been induced, it may be lifelong. More commonly, however, relapses occur months to years later. The relapses may also respond to re-treatment with topical clindamycin. Some patients who have very frequent relapses require continual biweekly intravaginal clindamycin or corticosteroids to remain in remission. Perimenopausal patients who are deficient in estrogen may require estrogen replacement as well as topical clindamycin to sustain a remission.

CERVICITIS

Etiology and Pathogenesis

Cervicitis is an inflammation that affects columnar epithelial cells of the endocervical glands but also can involve squamous epithelium of the ectocervix. Cervicitis may be infectious or noninfectious.[165] Infectious cervicitis is primarily caused by *N. gonorrhoeae, C. trachomatis,* or *M. genitalium.*[165]

Human papillomavirus, HSV, and *T. vaginalis* may involve the cervix but affect mainly the squamous epithelium of the ectocervix. Consideration of these important sexually transmitted organisms is beyond the scope of this chapter (see Chapters 135 and 143). Ureaplasmas and *Mycoplasma hominis* are organisms frequently found in the genital tract of women and men. Their etiologic role in disease has not been demonstrated. Noninfectious cervicitis is usually ectocervicitis, in which there is inflammation in an ectropion (Table 108.15). It is usually caused by mechanical or chemical irritation.

Symptoms and Diagnosis

The patient usually complains of a purulent vaginal discharge. The mucopurulent secretions are not irritating, so there is no vulvar discomfort or introital dyspareunia. In infectious cervicitis there may be dysuria, abnormal uterine bleeding, lower abdominal pain, or pelvic dyspareunia because gonococcal or chlamydial infection can involve the urethra, endometrium, or uterine adnexa. With noninfectious cervicitis, dysuria, abdominal pain, and deep (pelvic) dyspareunia are uncommon. There may be postcoital bleeding due to trauma to the inflamed ectropion during intercourse.

Findings on examination of the vulva and of the vaginal mucosa are usually normal. In infectious endocervicitis the purulent secretions can be seen to flow from the endocervical canal; in noninfectious ectocervicitis the purulent secretions can be seen to emanate from the ectropion (Fig. 108.16), often with clear normal secretions flowing from the endocervix. In some patients with noninfectious cervicitis the abnormal secretions are solely endocervical, presumably reflecting noninfectious endocervicitis. The other cardinal sign of cervicitis is sustained endocervical bleeding easily induced by minor trauma, such as touching the area with a swab (friability).[165] Vesicular lesions and ulcerations are present in HSV infection, whereas a strawberry cervix is characteristic of *T. vaginalis*.

In patients who have gonococcal, mycoplasmal, or chlamydial infection, urethral, uterine, or adnexal tenderness may be present, reflecting infection of these loci. The bimanual examination is usually normal in women who have noninfectious cervicitis.

Vaginal pH may be elevated. There is no odor when the secretions are mixed with 10% KOH. Wet preparations of vaginal secretions contain many leukocytes. The vaginal cells are mature. Gram-stained smears of cervical secretion confirm the presence of many leukocytes and, in gonococcal infection, may contain intracellular cocci.

In addition to microscopic examination, patients should be tested for *C. trachomatis* and *N. gonorrhoeae* by NAAT. These assays can be performed on vaginal/cervical or urine specimens. *T. vaginalis* antigen-based testing, or ideally, NAAT is also recommended.

Therapy

Studies that have attempted to correlate numbers of leukocytes in Gram-stained cervical smears with gonococcal or chlamydial infection have not produced clear-cut recommendations as to which patients should be treated for infectious cervicitis without waiting for culture results.

According to CDC guidelines, presumptive treatment with antimicrobials for *C. trachomatis* and *N. gonorrhoeae* should be provided for women with cervicitis who are at increased risk—those age younger than 25 years, those with a new sex partner, a sex partner with concurrent partners, or a sex partner who has an STI—especially if follow-up cannot be ensured.

Recommended regimens for presumptive therapy include azithromycin 1g orally in single dose or doxycycline 100 mg every 12 hours

for 7 days, and concurrent treatment for gonococcal infection (i.e., ceftriaxone 250 mg intramuscularly once plus azithromycin 1 g orally once) should be considered if the patient is at risk for gonorrhea or lives in a community where the prevalence of gonorrhea is high (>5%). For women with clinical evidence of cervicitis but at low risk for chlamydia or gonorrhea, therapy may be withheld while awaiting the results of diagnostic testing.

To minimize transmission and reinfection, women treated for cervicitis should be instructed to abstain from sexual intercourse until they and their partner(s) have been adequately treated (7 days after single-dose therapy or until completion of a 7-day regimen) and symptoms have resolved.

Patients who have positive tests for sexually transmitted bacteria should be treated with regimens recommended for the specific etiologic agent,[24] and they should be offered partner services and instructed to return 3 months after treatment for repeat testing because of high rates of reinfection. Treatment for *M. genitalium* with moxifloxacin might be considered for cases of clinically significant cervicitis that persist after azithromycin or doxycycline therapy and in which reinfection is unlikely.

Cervicitis in pregnant women can cause pregnancy and neonatal complications. Diagnosis and treatment of cervicitis in pregnant women does not differ from that in women who are not pregnant, although doxycycline should be avoided.

If tests for gonococci, *M. genitalium,* and chlamydiae are negative, antimicrobial treatment is not likely to be of benefit.

If the volume of secretions arising from an ectropion is bothersome, destruction of the endocervical mucosa of the ectropion with cryotherapy may allow the ectocervix to become reepithelialized with squamous epithelium, with a resultant diminution in the volume of ectocervical secretions.

ESTROGEN-DEFICIENCY VAGINITIS (GENITOURINARY SYNDROME)

Etiology and Pathogenesis

Estrogen-deficiency vaginitis is seen in postmenopausal women and in younger women who have become deficient in estrogen because of disease or because of treatment with pharmaceuticals that interfere with the production or the activity of estrogen.[166] This condition can also be seen during breastfeeding because of an effect of prolactin on estrogen production.[167] Without estrogen the genital mucosa thins. Glycogen is decreased, and, as a result, lactobacilli no longer dominate the vaginal microbial microbiota. Thinning of the mucosa may result in vulvar discomfort and introital dyspareunia. Symptoms include vaginal dryness, burning, irritation, dyspareunia, vulvar or vaginal bleeding, and vaginal discharge.

The thin vaginal mucosa may become infected, presumably by enteric organisms and others that are able to colonize the vagina in the absence of lactobacilli. Frequent UTIs may occur. In some instances estrogen-deficiency vaginitis overlaps with DIV.

Due to the just-described pathogenesis and involvement of the lower urinary tract, the term *genitourinary syndrome of menopause* has been linked to those symptoms.[168]

Diagnosis

The vestibular and vaginal mucosae are pale, often with patches of erythema. Vaginal secretions, if present, may be purulent. Vaginal pH is elevated. There is no odor when the secretions are mixed with 10% KOH. Microscopic examination of the secretions discloses immature (parabasal) vaginal cells with or without leukocytes. Vaginal cultures contain a variety of enteric and other bacteria.

Therapy

The primary indication for therapy is the presence of symptoms. Before initiation of therapy other causes should be excluded, such as UTI and endometrial cancer in patients with postmenopausal bleeding.

The primary defect is the absence of estrogen. Therefore definitive treatment involves estrogen replacement or cessation of antiestrogenic drugs or breastfeeding. Topical antibacterial agents containing sulfonamides or clindamycin may improve symptomatic vaginitis, and lubricating agents may relieve vaginal dryness and dyspareunia. Use of vaginal estrogen requires caution in women with high risk of estrogen-dependent tumors. In November 2016 FDA approved the use of Prasterone, another name for dehydroepiandrosterone 6.5 mg (0.5% formulation), for the treatment of genitourinary syndrome (vulvovaginal atrophy). The mechanism of action is due to aromatization of androstenedione and testosterone locally to estrol and estradiol. Ospemifene is a selective estrogen receptor modulator that acts as an estrogen agonist in the vagina. It is an oral therapy that can be used in women who cannot or prefer not to use vaginal product.

Without estrogen replacement, symptoms may recur after cessation of treatment.

VULVAR PAIN SYNDROME (FORMERLY VULVODYNIA, VESTIBULODYNIA, VULVAR VESTIBULITIS, OR FOCAL VULVITIS)

External genital discomfort is a very common symptom among women of reproductive age. Usually described as itching or burning, vulvar discomfort may or may not be associated with introital dyspareunia. There are a number of possible causes, few of which are infectious and virtually none of which are sexually transmitted. Nonetheless, the clinician should be aware of these entities to rule out infections, prescribe appropriate treatment if the diagnosis is apparent, and refer the patient to a gynecologist or dermatologist who specializes in vulvar disease if an explanation for the patient's symptoms is not readily forthcoming.

Definition and Terminology

In 2015 representatives from the International Society for the Study of Vulvovaginal Disease, the International Society for the Study of Women's Sexual Health, and the International Pelvic Pain Society developed consensus terminology and classified persistent vulvar pain into two categories[169]: (1) vulvar pain caused by specific disorder and (2) vulvodynia—vulvar pain of at least 3 months' duration, without clear identifiable cause, and that may have potential associated factors.

Vestibulitis has been eliminated from the updated terminology because the presence of inflammation (implied by "itis") has not been documented.

Vulular pain secondary to a specific disorder includes the following:
Infectious (e.g., recurrent candidiasis, herpes)
Inflammatory (e.g., lichen sclerosus, lichen planus, immunobullous disorders)
Neoplastic (e.g., Paget disease, squamous cell carcinoma)
Neurologic (e.g., postherpetic neuralgia, nerve compression, or injury, neuroma)
Trauma (e.g., female genital cutting, obstetrical)
Iatrogenic (e.g., postoperative, chemotherapy, radiation)
Hormonal deficiencies (e.g., genitourinary syndrome of menopause [vulvovaginal atrophy], lactational amenorrhea)

Vulvodynia can be as follows:
Localized or generalized or mixed
Provoked (insertional, contact), spontaneous, or mixed
Primary or secondary
Intermittent, persistent, constant, immediate, or delayed

Epidemiology

The prevalence of chronic vulvar pain (all types) ranges from 3% to 15% in self-report studies.[170] Assessing prevalence is challenging because many women with vulvar pain do not present for evaluation. In one study risk factors for the development of vulvodynia included younger age, Hispanic ethnicity, married, depression, posttraumatic stress disorder (PTSD), sleep dysfunction, and other chronic pain syndromes.[171]

Etiology and Pathogenesis

The infectious etiology of vulvar pain can be secondary to recurrent VVC, herpes, and sometimes trichomoniasis. The noninfectious etiologies of vulvodynia (localized or generalized) are not known and likely multifactorial.

Risk factors include the following:
Excessive inflammation, increase of proinflammatory products in the vulvar tissue

Neurologic proliferation and sensitization
Genetic factors via at least three potentially overlapping mechanisms: genetic polymorphisms that increase the risk of candidiasis or other infections, genetic changes that allow prolonged or exaggerated inflammatory responses, and increased susceptibility to hormonal changes associated with oral contraceptive pills
Hormonal factors: use of combined hormonal contraceptives
Psychological factors such as depression, anxiety, PTSD
Musculoskeletal and structural defect like pelvic floor muscle dysfunction, pelvic organ prolapse

Clinical Manifestations

The main complaint is significant pain upon contact with vulvar vestibule; other symptoms include irritation, raw sensation, and burning with or without dyspareunia.

Diagnosis

Sexually transmitted conditions, including genital ulcers and warts involving the labia majora and labia minora, should be obvious on physical examination. The only infection that commonly causes diffuse vulvitis is VVC, usually in association with involvement of the vestibule and vagina.

Vulvar pain syndrome (vulvodynia) is a clinical diagnosis based upon a detailed history and physical examination.

Diagnostic criteria include pain, absence of identifiable cause, duration of at least 3 months, pain with pressure point testing.[172] The latter is a cardinal sign confirmed by severe pain upon palpation of the vulva vestibule with a cotton-tipped swab or with the examiner's finger.

Laboratory evaluation is usually done to exclude other causes of the patient symptoms; vuvlvodynia does not cause laboratory abnormalities. Workup should include all other etiologies of vulvovaginitis; biopsy can be performed to exclude neoplastic and inflammatory causes such as lichen sclerosus.

Therapy

If an infectious cause is identified, it should be treated accordingly.

The treatment of vulvodynia involves a multidisciplinary approach, including psychological interventions, pelvic floor physical therapy, and vestibulectomy (for provoked vestibulodynia), and vulvar hygiene (avoiding soap or fragrance).

Treatment typically progresses from less invasive to more invasive, and several treatment options are worth pursuing.

Topical lubricants that moisturize the skin or reduce the friction during sexual contact are helpful. Medical therapy includes topical preparations such as lidocaine and estrogen cream and oral medications such as antidepressants, anticonvulsants, and injection therapy.

Submucosal injections of corticosteroids have a local antiinflammatory effect and appear to treat pain in women with vulvodynia.[173,174] Topical steroids are not recommended because of the lack of efficacy of low-dose corticosteroids and potential side effects of high-potency steroids.[175]

Of note, these treatment options are not specifically approved for vulvodynia and therefore represent off-label use.

Surgery is considered treatment of the last resort and usually not recommended. Laser therapy for vulvodynia is an area of developing research.[176]

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The complete reference list is available online at Expert Consult.

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