Bacterial and Mycotic Infections in Immunocompromised Hosts: Clinical and Microbiological Aspects

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Gynecological Infections in Immunocompromised Hosts

Bassam H Rimawi* and Ramzy H Rimawi†
†Department of Obstetrics and Gynecology, Section of Reproductive Infectious Diseases & Maternal Fetal Medicine, Medical University of South Carolina, South Carolina, USA
*Department of Internal Medicine, Section of Infectious Diseases, Travel Medicine and Critical Care Medicine, East Carolina University, North Carolina, USA
*Corresponding author: Bassam Husam Rimawi, Department of Obstetrics and Gynecology, Section of Reproductive Infectious Diseases & Maternal Fetal Medicine, Medical University of South Carolina, USA, Tel: (843) 792-7420, M: (845) 667-6364; E-mail: Rimawi@musc.com

Abstract

Genitourinary tract infections are among the most frequent disorders for which patients seek gynecologic care. The obstetrician and gynecologist must be persistently vigilant of unique opportunities to detect infections that may become serious and life threatening. The manifestations of gynecological infections can be devastating to many hosts, particularly in pregnant women who face challenges of preterm birth and low birth weight. The vaginal microbiome consists of a unique collaboration of mixed microorganisms, with Aerobic microorganisms being amongst the most in patients with normal vaginal flora, with an average of approximately six different species of bacteria, the most common of which are lactobacilli. With an intact immune system, these microorganisms act as a protectant against many cases of gynecological infections. Insults to the vaginal microbiome can lead to changes in vaginal pH, thereby increasing the host to a variety of different infections, including sexually transmitted diseases. These insults tend to manifest more commonly in immunocompromised hosts, which accounts for their higher rates of gynecological infections. Early recognition and treatment can improve outcome, but it requires an astute clinician to recognize the risk factors and subtle changes in presentation and laboratory analysis to assure that appropriate therapy is initiated. We present the etiologies, clinical manifestations, microbiology and latest treatment and diagnostic recommendations for gynecological infections in an immunocompromised host.

Keywords: Vaginitis; Sexually transmitted diseases; Immunocompromised; Infections; Sepsis; Toxic shock syndromes; Preterm birth; Low birth weight; Antibiotic therapy

Introduction

The diagnosis and treatment of female obstetric and gynecologic infections is a routine occurrence in the outpatient and hospital setting. Gynecologic infections originate within the female pelvis and can spread to near-by organs resulting in a wide spread disease process. These infections commonly occur in pregnancy and during postoperative periods. Gynecologic infections are a microbial phenomenon characterized by an inflammatory response to the presence of microorganisms or invasion of normally sterile host tissue. In many cases, these infections are transmitted via sexual intercourse. When unrecognized, or severe, these infections may result in bacteremia, sepsis, septic shock and death. The clinical manifestations of sepsis are caused by the body’s inflammatory response to toxins and other components of microorganisms [1].

Immunocompetent women seeking medical care have the advantage of having these infections readily diagnosed given their clinical manifestations and treated with prompt antimicrobial therapy. Immunocompetent hosts also have the advantage of clearing the infections more readily resulting in quicker recovery periods with less complicating sequelae.

Uncommon cases, such as those presenting in immunocompromised hosts, often fail to mount a proper immune response to gynecologic infections. This results in difficulty in early detection and an infectious process that may go unrecognized without a careful assessment of clues available through physical examination and laboratory testing. A recent study found that hydrogen peroxide plays a role in the immune system in certain fish and humans [2]. In the study, scientists found that hydrogen peroxide within cells increased after tissues were damaged in zebra fish, which is thought to act as a signal to white blood cells to converge on the site and initiate the healing process. When the genes required to produce hydrogen peroxide were disabled, white blood cells did not accumulate at the site of damage. The experiments were conducted on fish; however, because fish are genetically similar to humans, the same process is speculated to occur in humans. This explains why immunocompromised patients are less likely to clear many infections so readily, specifically gynecological infections. However, even with an intact functioning immune system, these vulnerable hosts may come in contact with virulent pathogens that can lead to severe infections, septic shock and death, despite acting apprehensively and appropriately.

Unfortunately, pregnancy itself harbors an immunocompromised state, thereby, increasing the likelihood of severe infections when a virulent microorganism is paired with an infectious procedure complication such as induced abortions, vaginal delivery, more especially with episiotomies and cesarean deliveries. Gynecological procedures, such as hysterectomies, with concomitant medical co-morbidities (i.e. diabetes mellitus) may further increase the likelihood of severe infections to occur [3]. Clinicians often rely on the basics of history and physical examination to guide further diagnostic workup and treatment of women presenting with complaints after these procedures.
The association between preterm birth and infection is well known and long established. Systemic infections such as pyelonephritis and pneumonia are associated with preterm delivery, but ascending vaginal infection may be the most common and critical pathway. Ascending microbes reach the membranes and amniotic fluid by ascending into the cervix and uterus from the vagina and incite an inflammatory response. This maternal immune activation (MIA) can result in unwanted consequences, such as preterm birth, neonatal brain injury and low birth weight [4].

Homelessness is a major global problem, with estimates of up to 100 million people worldwide being vagrant, of which at least 600,000 are in the United States. Homeless women are at a high risk for rape, commercial sex working and abusing illicit drugs, such as needles from other immunocompromised hosts with HIV and hepatitis [5]. In addition to becoming immunocompromised, they are less likely to seek medical attention for gynecological infections. This consequentially places them at a higher risk of complications, including bacteremia, sepsis, septic shock and death.

**Pathophysiology for Gynecological Infections**

It is important to understand the fundamental stages of infection, defined as a microbial inflammatory response to the presence of microorganisms or invasion of normally sterile host tissue [6]. Invasion results in exponentiation of pathogenic microorganisms in a bodily part or tissue, which may produce subsequent tissue injury that progresses to overt disease through a variety of cellular or toxic mechanisms. The following stages result from infections:

**Bacteremia**

- Presence of bacteria in the blood
- Risks factors include systemic diseases, such as meningitis or pneumonia, surgical procedures, catheters entering into the bloodstream and intravenous drug abuse
- Can spread hematogenously to other body organs and tissues, causing systemic disease
- An intact immune system may help clear this bacterial process efficiently, resulting in a quicker recovery with fewer overt complications.
- Constellation of symptoms including fever, chills, tachycardia and hypotension defines sepsis and septic shock

**Sepsis**

- Hyperthermia (>38.3°C) or hypothermia (<36°C)
- Tachycardia
- Tachypnea
- Altered mentation
- Significant edema or positive fluid balance (>20 mL/kg over 24-hours)
- Hyperglycemia in the absence of diabetes (plasma glucose >140 mg/dL)
- Clinical manifestations caused by the body's inflammatory response to toxins and other components of microorganisms

**Septic shock**

- Hypotension (systolic blood pressure <90 mmHg, or a reduction of 40 mmHg from baseline) with oliguria (<0.5 mL/kg/hr for ≥2 hours) despite adequate fluid resuscitation
- Azotemia with creatinine >2 mg/dL
- Thrombocytopenia (<100,000 µL)
- Hyperbilirubinemia (>2 mg/dL)
- Multiple organ dysfunction
- Perfusion abnormalities, including lactic acidosis (>1 mmol/L) and obtundation

The vaginal microbiome consists of a complex ecosystem harboring a mixed array of microorganisms [7]. *Lactobacilli* are the regulator of this ecosystem and the predominant bacteria of the vaginal tract. A healthy vaginal microbiome maintains an acidic pH (< 4.5), which inhibits the adherence of bacteria to the vaginal epithelial cells. Approximately 60% of *lactobacilli* produce hydrogen peroxide, which inhibits different microorganisms such as those in bacterial vaginosis, yeast infections and *Gardnerella vaginalis*. This may also destroy the *Human immunodeficiency virus* (HIV) in vitro [8]. Estrogen improves *lactobacilli* colonization by enhancing vaginal epithelial cell production of glycogen, which breaks down into monosaccharides and can then be converted to lactic acid. The acidic pH also inhibits the habitation of sexually transmitted pathogens, *Chlamydia trachomatis*, *Neisseria gonorrhoea* and *Trichomonas vaginalis* [9]. Other normally inhabiting microorganisms consist of *Aerobic* gram-negative and gram-positive bacteria, some of which harbor devastating toxins. Although these microorganisms tend to keep their toxins inactivated, severe gynecological infections can occur if they are activated.

Each year, over 6 million healthcare visits are due to some form of vaginitis, with more than a billion dollars spent annually on assessment and treatment. Bacterial vaginosis is perhaps the most common form of vaginitis, accounting for approximately 12-50% of occurrences [10]. According to the National Health and Nutrition Examination Survey (NHSES), a national population-based study of 12,000 women aged 14-49 years old who self-collected their own vaginal swabs were analyzed with the Nugent Gram stain criteria [11]. The prevalence of bacterial vaginosis was 29.2%. Non-Hispanic blacks accounted for 51.6%, Mexican Americans accounted for
32.1% and non-Hispanic Whites accounted for 23.2%. Despite adequate therapy, recurrent bacterial vaginosis is common, with up to 80% in some studies.

**Etiologic Causes of Gynecological Infections in Immunocompromised Hosts**

**Aerobic** gram-negative bacteria harbor endotoxins within a disaccharide core consisting of a lipoidal acylated glucosamide. Two highly conserved endotoxins found within gram-negative bacteria are lipid A and lipopolysaccharide (LPS) release cytokines (i.e., tumor necrosis factor α) and other immune modulators that mediate the clinical manifestations of sepsis. Aerobic gram-positive organisms mediate sepsis by 2 main mechanisms: (1) cell wall components, such as peptidoglycan, teichoic acids and surface proteins; (2) release of various toxins, both endotoxins and exotoxins, such as toxic shock syndrome toxin-1 released by *Staphylococcus aureus* [12].

In addition to organisms that may typically infect normal hosts, immunocompromised patients have increased susceptibility to infections with organisms of little native virulence in normal individuals. *Group A streptococcus* (GAS) is rarely present, but may harbor, the normal vaginal flora from inoculation of the women’s own pharynx or from a close contact source [13]. GAS is known to harbor a variety of virulence factors, such as M-protein, streptokinase, streptolysin S and O and streptococcal chemokine protease enzymes, which stimulate the release of interleukin-1, tumor necrosis factor α, interleukin-6 and arachidonate metabolites from human monocytes. These virulence factors result in clinical invasive GAS gynecological infections, such as postpartum endometritis, wound infections, necrotizing fasciitis and toxic shock syndrome. The differential diagnoses of the potential microbes that lead to gynecological infections in immunocompromised host are broad and may include:

1. Encapsulated bacteria, such as *Group B streptococcus* (GBS) is of great concern, specifically during the immunocompromised state of pregnancy, which is known to cause infections in both the mother and her newborn child. In the mother, GBS is associated with vaginitis, cervicitis, endometritis, sepsis, meningitis and pneumonia, whereas in the newborn, GBS is associated with conjunctivitis, meningitis, pneumonia and sepsis. During pregnancy, chorioamnionitis can be also seen with GBS.

2. **Aerobic** bacteria— *Neisseria gonorrhoeae*, *Staphylococcus*, *Streptococcus*, *E. coli*, *Mycoplasma genitalium*, *Haemophilus ducreyi* and *Klebsiella granulomatis*

3. **Anaerobic** bacteria— *Chlamydia trachomatis*, *Trichomonas vaginalis*, *Listeria monocytogenes*, *Gardnerella vaginalis*, *Peptostreptococcus*, *Prevotella brevis*, *Mobiluncus*, *Mycoplasma species*, *Clostridium*, *Haemophilus ducreyi*, *Actinomyces israelii* and *Bacteroides*

4. Spirochete— *Treponema pallidum*

5. Yeast— *Candida albicans*

6. Viral—Herpes Simplex, *Human papilloma virus* (HPV), *Human immunodeficiency virus*

**Clinical Approach to Gynecological Infections**

Vaginal discharge is the most commonly reported symptom in a patient presenting with an acute gynecological infection. It is important for a clinician to differentiate normal from abnormal vaginal secretions, a factor that often leads to unnecessary treatment. Normal vaginal secretions are composed of vulvar secretions from sebaceous, sweat, Bartholin and Skene glands, exfoliated vaginal and cervical cells, cervical mucus, endometrial and ovudital fluids, and microorganisms with their metabolic products. Normal vaginal secretions can be described as floccular in consistency, whitish in color, and usually located in the dependent portion of the vagina, posterior fornix. A wet-mount can be used to analyze these normal vaginal secretions, in which the predominance of superficial epithelial or squamous cells can be noted along with a few white blood cells. However, a wet-mount can also be used to analyze clue cells, a cell-specific entity found with bacterial vaginosis and *Gardnerella vaginalis*. The adherence of bacteria can often be seen obliterating the crisp cell border of these epithelial cells microscopically. Gram stain reveals normal superficial epithelial cells and a predominance of gram-positive rods (i.e., *lactobacilli*) [14].

In immunocompromised patients with severe gynecological infections, the criteria for diagnosis of sepsis and systemic inflammatory response syndrome are rather modest. History and physical examination may be insufficient to identify a life-threatening infection. Differentiating sepsis caused by gram-positive versus gram-negative organisms clinically can be very challenging. In general, certain risk factors that increase a woman’s risk of acquiring a gynecological infection include promiscuous, unprotected sexual behavior, multiple sexual partners and history of prior sexually transmitted diseases. These risk factors are detrimental in immunocompromised hosts as they have a reduced ability in clearing an infection, thereby, resulting in a higher tendency to progress to a life-threatening infection.

A careful history and physical examination is crucial when patients present with complaints of vaginal discharge, irritation, odor, pelvic lesions or ulcers, pelvic/abdominal pain, fever, chills, malaise and muscle ache. Office-based testing can detect and diagnose many of the gynecological infections, such as bacterial vaginosis, *Trichomonas*, vulvovaginal candidiasis, inflammatory and atrophic vaginitis, cervicitis, pelvic inflammatory disease, and genital ulcer (vulvar) diseases, such as chancroid, *herpes*, syphilis and genital warts. Women account for approximately 40-50% of all newly diagnosed HIV hosts, with intravenous drug use and heterosexual transmission being responsible for the most cases of acquired immunodeficiency syndrome (AIDS) in the United States [15]. It is worth noting that although these infections are generally more commonly seen in immunocompromised patients, they can be seen at any immune states.

**Vaginal infections**

The normal vaginal flora is comprised of an ecosystem of different microorganisms, most commonly *lactobacilli*, maintaining an acidic environment (pH 3.8-4.5) to inhibit the inhabitation of many pathogenic organisms [16]. Bacterial vaginosis (BV) is the most common form of vaginitis in the United States, in which the normal vaginal bacterial flora is being affected and replaced by an overgrowth of predominantly Anaerobic bacteria, such as *Gardnerella vaginalis* and *Mycoplasma hominis*, due to the loss of hydrogen peroxide-producing *lactobacilli*. Unfortunately, we have not been able to understand what exactly causes this disturbance of normal vaginal flora. Some experts have postulated that repeated alkalinization of the vagina, which occurs with frequent sexual intercourse...
or use of douches plays a role [17]. BV is therefore considered to be a sexually “related” disease rather than sexually transmitted disease. Untreated or immunocompromised women are more likely to suffer from significant adverse sequelae due to BV, such as pelvic inflammatory disease, particularly after induced abortions and hysterectomies, resulting in postoperative cuff infections and abnormal cervical cytology. Pregnant women, especially those severely immunocompromised, are at high risk for premature rupture of membranes, preterm labor and delivery, chorioamnionitis and post-cesarean endometritis [18]. See Section 4.4 for diagnostic algorithm and Section 4.5 for treatment.

*Trichomonas* vaginitis is a sexually transmitted disease associated with an *Anaerobic* flagellated parasitic microorganism known as *Trichomonas vaginalis*. In many occasions, immunocompromised patients who contract this infection often have other concomitant gynecological infections, including BV, *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, syphilis and HIV [19]. As with BV, immunocompromised patients with *Trichomonas* vaginitis left untreated or undertreated are at an increased risk of postoperative cuff cellulitis following a hysterectomy. Every patient scheduled to have a hysterectomy, whether via vaginal, abdominal, or minimally invasive technique, should have testing and treatment of *Trichomonas* and BV prior to their surgery. Immunocompromised pregnant patients also carry an additional risk of premature rupture of membranes and preterm delivery. Studies have shown that patients who acquire *Trichomonas* have a three times increased likelihood of acquiring HIV. Immunocompromised patients also carry an additional risk of acquiring chronic HPV infections, which can ultimately increase their risk of cervical cancer [20]. According to the CDC guidelines, all immunocompromised hosts should be tested for *Trichomonas* annually [21]. Immunocompromised hosts, such as those with HIV, who are infected with *Trichomonas vaginalis*, should be treated with a 7-day course of metronidazole; rather than a one-time dose of 2 grams orally as done with HIV-negative patients. For non-pregnant patients, a test of cure should be performed 3 months after receiving therapy, as well as testing, diagnosing and treating all partners involved. Immunocompromised hosts who have an allergy to metronidazole should be treated with a desensitization protocol; whereby, they are hospitalized and treated with escalating doses of metronidazole or tinidazole under close observation. See Section 4.4 for diagnostic algorithm and Section 4.5 for treatment.

Vulvovaginal candidiasis (VVC) is very common in immunocompromised patients, with estimates of at least 75% of hosts experiencing at least one episode during their lifetimes and over 50% of these hosts having recurrent infections even after adequate therapy [22]. Immunocompromised patients have the advantage of clearing their primary infection more readily with few having recurrent infection. *Candida albicans*, a dimorphic fungus that exists as a blastospore, has the ability to transform into mycelia as a result of blastospore germination. This transformation gives this fungus the ability to colonize the lower genital tracts of many immunocompromised hosts without any symptoms; however, tissue invasion may ultimately incur. When the invasion process occurs, these fungi are capable of releasing extracellular toxins, which accounts for the symptoms of pruritus and inflammation surrounding their lower genital tracts [23]. *Candida albicans* is responsible for at least 90% of vaginal yeast infections, which respond well to most over-the-counter antifungal vaginal suppository agents. For this reason, it is critical that a proper work-up with fungal cultures be performed when immunocompromised patients present with symptoms of VCC. *Candida glabrata* and *Candida krusei* have been known to be resistant to many traditional antifungal agents. The most vulnerable immunocompromised hosts that suffer from recurrent symptomatic disease, defined as ≥ 4 per year, include patients with advanced or uncontrolled HIV, diabetes mellitus, pregnancy and chronic antibiotic use. Most experts agree that the main reason for their recurrent disease is their inability to mount a proper cell-mediated immunity, thereby, leading to a higher incidence of candidiasis [24]. See Section 4.4 for diagnostic algorithm and Section 4.5 for treatment.

Other forms of vaginitis more commonly seen in immunocompromised hosts include inflammatory vaginitis, a clinical syndrome characterized by diffuse exudative vaginitis, epithelial cell exfoliation, and a profuse purulent vaginal discharge [25]. As with most forms of vaginitis, a lack of lactobacilli is seen and replaced with gram-positive cocci, usually *streptococci*. Their symptoms of vulvovaginal burning or irritation are most apparent after sexual intercourse. Clinicians often confuse this condition with atrophic vaginitis, a condition that presents with purulent vaginal discharge and an inflamed vagina. Of importance with immunocompromised hosts suffering from atrophic vaginitis, patients not only lack estrogen resulting in an atrophic vagina as seen with menopausal women or after removal of patient’s ovaries, but they also have a decrease in glycogen breakdown into monosaccharides by vaginal epithelial cells. This reduces the production of lactic acid by *lactobacilli*, thereby, reducing their ability to readily clear their gynecological infections.]

**Pelvic infections**

The normal anatomy of the human cervix is divided into an ectocervix and an endocervix, each with its own specific cell type attracting different gynecologic infections to their cell type [26]. For example, *Neisseria gonorrhoeae* and *Chlamydia trachomatis* typically infect the glandular layer of the endocervix, whereas *Trichomonas, Candida species* and herpes *Simplex virus* infect the epithelial layer of the ectocervix. Immunocompromised hosts have a higher tendency to develop ascending vaginal infections leading to pelvic complications, such as pelvic inflammatory disease (PID). Moreover, immunocompromised hosts are more likely to have recurrent infections that not only are a major cause of chronic pelvic pain, but are also a leading cause of infertility secondary to scarring of fallopian tubes [27]. Treatment options for *Neisseria gonorrhoeae* and *Chlamydia trachomatis* will be discussed in Section 4.5. There has been an increase in antibiotic resistance with *Neisseria gonorrhoeae*. The current CDC recommendations are a combination of ceftriaxone plus azithromycin or doxycycline for 7 days [21]. As with *Trichomonas vaginalis*, non-pregnant patients will need a test of cure 3 months after receiving therapy, as well as testing, diagnosing and treating all partners involved. See Section 4.4 for diagnostic algorithm and Section 4.5 for treatment.

Pelvic inflammatory disease is a condition that is caused by ascending microorganisms from the endocervix, most commonly *Neisseria gonorrhoeae* and *Chlamydia trachomatis*, through the endometrium of the uterus and through the fallopian tubes to the pelvis [28]. This inflammation being present at any point along a continuum that includes endometritis, salpingitis and peritonitis explains the pelvic pain associated with uterine tenderness and cervical motion tenderness. In immunocompromised patients, there is more residual disease within any point in route due to a decreased ability to readily clear their primary infection. There is a higher frequency of PID caused by other microorganisms, such as *prevotella, peptostreptococci* and *Gardnella vaginalis* [29]. See Section 4.4 for diagnostic algorithm and Section 4.5 for treatment.

End-stage PID can often lead to the development of a life-threatening tubo-ovarian abscess in immunocompromised patients. This abscess can involve either one or both adnexa, filling them with purulent fluid, which on radiological studies, appears as complex masses resembling ovarian malignancies. Disseminated disease is often seen with immunocompromised hosts, encompassing nearby organs
such as bowel and urinary bladder. Due to the nature of this wide spread disease, they are more likely to fail antibiotic therapy, resulting in the need for surgical intervention. In these cases, a failure to intervene surgically can lead to a catastrophic sequel of complications and ultimately wide spread sepsis, septic shock and even death [30].

Genital ulcer (Vulvar) infections

Promiscuous sexual behavior with multiple sexual partners and failure to use condom contraception, as well as a prior history of sexually transmitted diseases are the leading causes of genital ulcers caused by herpes Simplex virus (HSV) and syphilis in the United States. Immunocompromised patients also have the added list of acquiring additional ulcers, such as chancreid, caused by Haemophilus ducreyi, lymphogranuloma venereum (LGV) caused by Chlamydia trachomatis serovars L1, L2, L2a or L3, and granuloma inguinale (donovanosis) caused by Klebsiella granulomatis [31]. A thorough physical examination and history is crucial when assessing a patient with a genital ulcer(s). Optimally, the evaluation of a patient with a genital ulcer should include dark-field microscopy or direct immunofluorescence test for Treponema pallidum, culture of antigen testing for HSV, and culture for Haemophilus ducreyi. Many immunocompromised hosts, particularly those who are homeless or seek very little medical attention, develop genital ulcers begin as small ulcers with time and expand and encompass nearly their entire genital area with time. Of note, approximately ¼ of these diagnoses remain unconfirmed.

Herpes Simplex is a viral disease from the herpesviridae family caused by both Herpes Simplex Virus type 1 (HSV-1) and type 2 (HSV-2). Infection with the herpes virus is categorized into one of several distinct disorders based on the site of infection. Transmission may also occur via skin contact during periods of asymptomatic shedding. Condom contraception has been shown to decrease transmission rate [31]. Recurrent infections may occur more especially with immunocompromised hosts. These hosts also have higher tendencies to have more outbreaks related to a variety of stimuli and stressors, such as more frequent bacterial and viral infections, other sexually transmitted diseases and longer recovery periods from prior infections [32]. Grouped vesicles mixed with small ulcers, particularly with a history of such lesions, are almost always pathognomonic of genital herpes. Due to the broader range of tissue, the psychological aspect that follows such ulcers alters their self-image and affects their perceived ability to enter new sexual relationships and bear children. Of all the tests available for making a diagnosis of HSV, culture remains the most sensitive and specific test, with sensitivities reaching as high as 100% and specificities as high as 89% in the pustular stage. However, outside the pustular stage, genital PCR remains the test of choice in making the diagnosis of HSV [33].

Immunocompromised patients may have higher false-negative results with HSV cultures, especially with recurrent disease. Therefore, the use of type-specific immunoglobulin assays (IgG and IgM) for both HSV 1 and 2 is more useful in making the diagnosis of genital herpes. Direct fluorescent antibody testing (DFA) can also be used in establishing a diagnosis, which has similar sensitivities to a culture. However, the sensitivity and specificity drops by at least 50% in patients who have genital ulcers 3 or more days after the initial eruption of the lesions. Studies have shown that immunocompromised hosts are at high risk for resistant HSV to standard therapy with either acyclovir or valacyclovir, with reports indicating at least 5-15% of HIV positive patients (1% of the entire population) having resistance [34]. Sensitivities for acyclovir, ganciclovir, foscamet and cidofovir should be tested in cases with suspected HSV resistance. See Section 4.5 for treatment.

Another common sexually transmitted infection more commonly seen in immunocompromised hosts is syphilis. Women who acquire syphilis, caused by the spirochete bacterium Treponema pallidum, during pregnancy, particularly during the first trimester are at higher risk for transmitting the infection to the fetus, resulting in congenital syphilis [35]. With four different stages of syphilis, the signs and symptoms vary with each stage. The primary stage classically presents with a single, firm, painless, non-itchy chancre. Secondary syphilis involves a diffuse rash frequently involving the palms and soles. Latent syphilis may present with little to no symptoms while tertiary syphilis may present with gummus, neurological, or cardiac symptoms. There are two available sensitive tests used for diagnosing this infection, a nonreponeral rapid plasma reagin test (RPR) and a venereal disease research laboratory (VDRL) test. If any of these tests are positive, a confirmation should be followed, using either a fluorescent treponemal antibody absorption test (FTA ABS) or a microhemagglutinin-T. pallidum test (MHA TP) [36]. Patients with an elevated RPR titer and neurologic symptoms should undergo a lumbar puncture to rule out neurosyphilis. Treatment of syphilis in an immunocompromised pregnant host is penicillin. If a penicillin allergy is reported, penicillin desensitization should be done. See Section 4.5 for treatment.

Following HSV and syphilis, the next most common sexually transmitted disease most commonly presenting in an immunocompromised host is a chancroid, caused by the fastidious gram-negative streptobacillus, Haemophilus ducreyi. It is found primarily in developing countries and is most prevalent in low socioeconomic groups and commercial sex workers [37]. Infection initiates with microabrasions on the skin incurred during sexual intercourse. A local tissue reaction leads to development of an erythematous papule, which progresses to a pustule in 4–7 days and then undergoes central necrosis to ulcerate. Unlike primary syphilis, the ulcer(s) with this disease are painful and accompanied with lymphadenopathy, a gray or yellow discharge exudate and have soft edges. Diagnosis can be made using several methods, including PCR-based identification techniques. The most common method is culture from the bubo pus or ulcer secretions to identify H. ducreyi using microscopy [38]. See Section 4.5 for treatment.

Lymphogranuloma venereum (LGV) is a sexually transmitted disease caused by Chlamydia trachomatis serovars L1, L2, L2a or L3. As with chancreid, microabrasions within the skin allows for this organism to enter, particularly in an immunocompromised host, whereby, it crosses the epithelial cell layer of mucous membranes. From there, the organism travels from the site of inoculation, down the lymphatic channels, to multiply within mononuclear phagocytes of the lymph nodes. In the first week after exposure, a painless genital ulcer arises. In immunocompetent hosts, it tends to heal spontaneously within a few days [39]. However, in immunocompromised hosts, these ulcers may persist longer and less often resolve spontaneously. After one to six months from the initial stage, an untreated ulcer arises. In immunocompetent hosts, it tends to heal spontaneously within a few days [39]. However, in immunocompromised hosts, particularily those who are homeless or seek very little medical attention, develop genital ulcers begin as small ulcers with time and expand and encompass nearly their entire genital area with time. Of note, approximately ¼ of these diagnoses remain unconfirmed.

Granuloma inguinale (donovanosis) is a sexually transmitted infection commonly affecting immunocompromised hosts caused by Klebsiella granulomatis. Painless single or multiple genital ulcers often present one week to one month after exposure. This ultimately progresses to destruction of the internal and external tissues. In immunocompromised hosts, this destruction results in extensive leakage of mucus and blood from the highly vascular lesions. These hosts are also at high risk of acquiring superinfection by other pathogenic
microbes, due to the destructive nature of donovanosis. The infection spreads, continuously damaging the infected tissue until treated. Diagnosis is made via proper sexual history and physical examination revealing a painless, beefy-red ulcer with a characteristic rolled edge of granulation tissue. In contrast to syphilitic ulcers, inguinal lymphadenopathy generally is absent. Tissue biopsy and Wright-Giemsa stain are used to aid in the diagnosis to look for the presence of Donovan bodies in the tissue sample [41]. See Section 4.5 for treatment.

Condyloma accuminata are external genital warts that are related to an infection with the human papillomavirus infections (HPV), nononcogenic types 6 and 11. In women, these lesions tend to affect the posterior forchette and the lateral areas of the vulva, areas most directly affected by coitus. Immunocompromised patients may also have these warts extending throughout their vulva, vagina and cervix. Microabrasions on the skin allows for transmission to occur from an infected individual, as the viral particles begin to replicate and produce a wart. The more lesions present, the higher the chance that transmission from one person to another can occur. If not treated by excision of the warts and evaluation for other types of HPV strains that may be present, these immunocompromised hosts are at high risk of developing gynecological malignancies, including vulvar, vaginal and cervical cancers. These hosts are also at higher risk for recurrences secondary to a reactivation of the subclinical infection [42]. Treatment typically consists of excision, as eradication of the viral infection is not possible. Practicing safe sexual behavior can decrease the risk of primary and recurrent HPV infections. See Section 4.5 for treatment.

**Section 4.4: Diagnostic Algorithm for Gynecological Infection.**

### Vaginal Infections

<table>
<thead>
<tr>
<th>Disease</th>
<th>Microorganism(s) Involved</th>
<th>Preferred Treatment</th>
<th>Alternative Treatment</th>
</tr>
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<tbody>
<tr>
<td>Bacterial Vaginosis</td>
<td>1) Gardnerella vaginalis 2) Prevotella 3) Peptostreptococcus</td>
<td>Metronidazole 500 mg PO BID x 7 days</td>
<td>Clindamycin 300 mg PO BID x 7 days</td>
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<td>4) Mobiluncus 5) Bacteroides 6) Mycoplasma Species</td>
<td>Metronidazole Gel 0.25%, one applicator (5 gm) intravaginally once or twice daily for 5 days</td>
<td>Clindamycin Cream 2%, one applicator (5 gm) intravaginally for 7 days</td>
</tr>
<tr>
<td><strong>Trichomonas</strong></td>
<td>Trichomonas vaginalis</td>
<td>Metronidazole 500 mg PO BID x 7 days</td>
<td>Metronidazole 2 gms Po daily x 5 days</td>
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<tr>
<td></td>
<td></td>
<td>Metronidazole Gel is not effective against Trichomonas</td>
<td>Clindamycin 2gms PO daily x 5 days</td>
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<tr>
<td>Vulvovaginal Candidiasis</td>
<td>1) Candida albicans 2) Candida glabrata 3) Candida tropicalis</td>
<td>Fluconazole 150 mg PO x 1 dose after first dose for complicated cases plus hydrocortisone cream 1% to help relieve external irritation</td>
<td>Topical Agents</td>
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<td>Cinzolamizone</td>
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<td>- 1% cream, 5 gm intravaginally for 7-14 days</td>
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<td>- 100 mg vaginal tablet for 7 days</td>
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<td>- 100 mg vaginal tablet, 2 per day for 3 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- 500 mg vaginal tablet x 1 dose</td>
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<td></td>
<td></td>
<td></td>
<td>Butoconazole</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- 2% cream, 5 gm intravaginally for 3 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- 2% cream, 5 gm BI-BSR, single intravaginal application</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Nystatin</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- 100,000 units vaginal tablet Daily for 14 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Ticonazol</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- 6.5% ointment, 5 gm intravaginally x 1 dose</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Terconazol</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- 0.4% cream, 5 gm intravaginally for 7 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- 0.8% cream, 5 gm intravaginally for 3 days</td>
</tr>
</tbody>
</table>
Pelvic Infections

<table>
<thead>
<tr>
<th>Disease</th>
<th>Microorganism(s) Involved</th>
<th>Preferred Treatment</th>
<th>Alternative Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gonococcal Infections</strong></td>
<td>Neisseria gonorrhoeae</td>
<td>Ceftriaxone 250 mg IM x single dose + Azithromycin 1 gm orally x single dose OR Doxycycline 100 mg PO BID x 7 days</td>
<td>Ceftriaxone 400 mg PO x single dose + Azithromycin 1 gm orally x single dose OR Doxycycline 100 mg PO BID x 7 days</td>
</tr>
<tr>
<td><strong>Chlamydial Infections</strong></td>
<td>Chlamydia trachomatis</td>
<td>Azithromycin 1 gm orally OR Doxycycline 100 mg PO BID x 7 days</td>
<td>Cefixime 400 mg PO x single dose + Azithromycin 1 gm orally x single dose OR Doxycycline 100 mg PO BID x 7 days</td>
</tr>
</tbody>
</table>

**Pelvic Inflammatory Disease**

| 1) Neisseria gonorrhoeae         |                           | Outpatient Treatment Regimen A Ceftriaxone 250 mg IM x single dose OR Cefoxitin 2 gm IM + Probenecid 1 gm + Doxycycline 100 mg PO BID x 14 days +/- Metronidazole 500 mg PO BID x 14 days Regimen B Ofloxacin 400 mg PO BID x 14 days OR Levaquin 500 mg PO Daily x 14 days | Inpatient Treatment Regimen A Cefoxitin 2 gm IV every 6 hours OR Ceftetan 2 gm IV Q12 hours + Doxycycline 100 mg PO/IV Q12 hours Regimen B Clindamycin 900 mg IV Q 8 hours OR Gentamicin OR Ceftriaxone 1-2 gram IV Q 24 hours |
| 2) Chlamydia trachomatis         |                           |                           |                       |

**Must evaluate, diagnose and treat all partner(s) involved.**

Trichomonas Infection: Test of Cure should be performed 3 months after receiving treatment.

Chlamydial Infection: Test of Cure should be performed 3 months after receiving treatment; Cephalosporin Allergy: give Azithromycin 2gm orally in a single dose.

Pelvic Inflammatory Infection: hospitalization to treat PID may be recommended if the woman (1) is severely ill (e.g., nausea, vomiting, and high fever); (2) is pregnant; (3) does not respond to or cannot take oral medication and needs intravenous antibiotics; (4) has an abscess in the fallopian tube or ovary (tubo-ovarian abscess); or (5) needs to be monitored to be sure that her symptoms are not due to another condition that would require emergency surgery (e.g., appendicitis). If symptoms continue or if an abscess does not go away, surgery may be needed.

Denotations:

IM: Intramuscular; IV: Intravenously; BID: Twice Daily; TID: Three Times Daily; QID: Four Times Daily; PO: Orally

Genital Ulcer (Vulvar) Infections

<table>
<thead>
<tr>
<th>Disease</th>
<th>Microorganism(s) Involved</th>
<th>Preferred Treatment</th>
<th>Alternative Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Herpes</td>
<td>Herpes Simplex Virus</td>
<td>First Episode</td>
<td>Recurrent Episode</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Acyclovir 400 mg PO TID OR Famciclovir 250 mg TID OR Valacyclovir 1 gm PO BID 7-10 days</td>
<td>Acyclovir 500 mg PO BID OR Famciclovir 250 mg BID OR Valacyclovir 1 gm PO daily</td>
</tr>
<tr>
<td>Syphilis</td>
<td>Treponema pallidum</td>
<td>Primary, Secondary and &quot;Early Latent Disease Benzathine Penicillin G 2.4 million units IM in a single dose &quot;Late Latent Syphilis Doxycycline Benzathine Penicillin G 2.4 million units IM weekly x three doses</td>
<td></td>
</tr>
<tr>
<td>Chanroid</td>
<td>Haemophilus ducreyi</td>
<td>Azithromycin 1 gm PO x 1 dose</td>
<td>Ceftriaxone 250 mg IM x 1 dose OR Ciprofloxacin 500 mg PO BID x 3 days OR Erythromycin 500 mg PO QID x 7 days</td>
</tr>
<tr>
<td>Granuloma inguinale (donovanosis)</td>
<td>Klebsiella granulomatis</td>
<td>Doxycycline 100 mg PO BID x 3 weeks +/- Gentamicin if no improvement</td>
<td>Azithromycin 1 gm PO weekly x 3weeks Ciprofloxacin 750 mg PO BID x 3 weeks Erythromycin 500 mg PO QID x 3 weeks Trimethoprim-Sulfamethoxazole Double-Strength (160 mg/800 mg) BID x 3 weeks</td>
</tr>
<tr>
<td>Condyloma acuminata</td>
<td>Human Papillomavirus</td>
<td>Excision of Warts using either: - Trichloroacetic acid - Electrodesiccation - Cautery - Laser - Cryotherapy - Imiquimod 5% cream - Podophyllin 10-25% - Podofilox 0.5% - Interferon</td>
<td></td>
</tr>
</tbody>
</table>

*Early Latent Syphilis – defined at the first year of latent syphilis
*Late Latent Syphilis – defined as beyond 1 year of latent syphilis

Section 4.5: Antimicrobial Therapy for Gynecological Infections.
Special Considerations: HIV

Women account for approximately 40-50% of all individuals infected with HIV. Although HIV itself is not a gynecological disease, it is a cause of immunosuppression that can be transmitted via sexual intercourse. In the United States, intravenous drug use and heterosexual transmission are responsible for most of the cases of acquired immunodeficiency syndrome (AIDS) in women [43]. The interval progression time from HIV to AIDS is variable. A range of different infections have been linked with advanced HIV, including cryptococcosis, tuberculosis and *Pneumocystis jirovecii* pneumonia, formally known as Pneumocystis carinii pneumonia (PCP). As a result of this broad spectrum of infections, the initial evaluation of an HIV-positive woman includes screening for diseases associated with HIV, administration of recommended vaccinations (hepatitis A/B, pneumococcal and influenza), and behavioral and psychosocial counseling. HPV lesions, as with intraepithelial neoplasia, occur more frequently in HIV-positive women. For this reason, annual pap smears starting at the age of 21 years old is recommended [44]. Some non-randomized, non-blinded studies found that HIV-positive women who are virologically suppressed follow a similar course of HPV related infectious progression in the genital tract [45]. However, current recommendations still recommend annual pap smears in all HIV-positive women, irregardless of their HIV viral load [46]. As mentioned in the previous sections, immunocompromised hosts, such as those with HIV, tend to have a decreased ability to clear most acute gynecological infections readily and adequately, and in turn, face higher risks of complications secondary to disease-progression sequelae. In general, all gynecological infections should always be addressed and treated promptly to decrease morbidity and mortality, keeping in mind that recurrences are very common in patients who have a dysfunctional immune system.

Conclusion

With an intact functioning immune status, the majority of gynecologic infections can be diagnosed and treated effectively with few recurrences. However, immunocompromised hosts with untreated gynecologic infections have an increased morbidity and mortality rate. The major advantage of an intact immune system is the ability to clear an infection readily and adequately. The inability to mount a proper cell-mediated immune response can be detrimental to immunocompromised hosts. Healthcare providers should be keen to the likelihood of infections with ordinarily less virulent organisms during immunocompromised states and be able to adequately manage their infections in order to reduce relapses, complications, morbidity and mortality.

References


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