Sexually Transmitted Infections in Adolescence and Young Adulthood

A Practical Guide for Clinicians

Sophia A. Hussen
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Preface

Sexually transmitted infections (STIs) disproportionately impact adolescents and young adults in the United States and worldwide. The reasons for the differential impact of STIs on youth are myriad and complex. It is biologically and developmentally expected for sexual exploration to occur during the teenage and young adult years, as youth experience puberty and transition into independence in different parts of their lives. At the same time, adolescent and young adulthood can be fraught with biological, psychological, and social vulnerabilities that enhance susceptibility to STIs. While sexual desire, peer pressure, and other strong forces encourage sexual activity in this age group, youth are still developing their skills of abstract reasoning and may feel invincible to the consequences of their actions. Additionally, decades of research have shown that sexual education programming in most places is far from comprehensive, so that youth are at an informational disadvantage as well. Sexuality in youth and STI symptoms are also frequently stigmatized in society, so that youth may be uncomfortable seeking information or healthcare in this realm. On a more optimistic note, however, adolescents and young adults are still at a life stage in which they are educable, impressionable, and open-minded with regard to sexual and health protection behaviors. For all of these reasons, clinicians who care for adolescents and young adults with STIs encounter youth at a critically important juncture where nonjudgmental, clearly communicated STI education and counseling have the potential to be most impactful.

Effective diagnosis, treatment, and prevention of STIs in adolescence and young adulthood are complex tasks for any healthcare provider. This work requires mastery of several key skillsets, including but not limited to the following: (1) an understanding of the epidemiology and pathophysiology of the myriad infectious organisms that cause STIs; (2) clinical pattern recognition skills and biomedical knowledge of the requisite differential diagnoses; and (3) knowledge of adolescent development and an accompanying ability to communicate safer sex messaging effectively to youth across the adolescent/young adult age spectrum. Often, different groups of clinicians are more effective in one of these domains but not others. For example, primary care pediatricians, depending on the setting, may be uncomfortable making STI diagnoses and may struggle with balancing their relationships

with patients and their parents. Adult-oriented infectious disease physicians or STI clinic providers, on the other hand, may be more comfortable with the specific pathogens and their antibiotic resistance patterns but are likely to have little to no training on developmentally appropriate approaches to treating adolescents and young adults. This book was conceived with these diverse perspectives in mind and aims to include a range of chapters that will be useful for learners with different strengths and weaknesses.

STIs in adolescence and young adulthood also present important moral issues. For one, as will be noted throughout the different chapters, significant health inequities are present in youth STI epidemiology. Due to structural barriers in healthcare systems and society at large, racial/ethnic and sexual minority youth are often at higher risk for acquiring STIs yet may be less likely to present for treatment. The treatment and prevention of STIs therefore represent critically important avenues for addressing health inequities impacting vulnerable populations. Of note, in this book, we make specific efforts to note special considerations for particularly marginalized groups of adolescents, including pregnant youth, sexual minority youth, and youth living with HIV.

In summary, this book attempts to create a holistic yet practical reference that addresses epidemiological, biological, and ethical considerations in caring for adolescents and young adults presenting with, or at risk for, STIs. The first section presents general considerations in the care of sexually active adolescents, with a focus on broader issues impacting this age group and general principles to keep in mind when evaluating youth in the clinical setting. This section includes several chapters that are unique for clinically oriented texts such as this one – including one focused on racial and ethnic disparities and another focused on ethical and legal considerations in STI treatment for adolescents. The second section describes STIs by clinical syndrome (e.g., vaginitis, proctitis) and specifically includes extragenital manifestations of STI including proctitis, pharyngitis, and dermatoses. Finally, the third section takes a pathogen-oriented approach and describes the major bacteria, viruses, and parasites responsible for the most common STIs. Obviously, there is overlap in content between some of the chapters – e.g., chlamydia is discussed in a pathogen-focused chapter but also in the syndrome-focused chapters focused on vaginitis, PID, urethritis, and proctitis. As such, the chapters can stand alone or be read all together, depending on the goals of the reader at the time.

There are several caveats and limitations that should be noted. First, this book is written from the perspective of practitioners based in the United States to a US-based audience. While some principles will be transferable across cultural and geographic contexts, there are also critical differences in conceptualizations and lived realities of adolescence around the world, and our recommendations cannot always be generalized to other settings. Second, although the chapters' authors have made their best efforts, adolescent-specific epidemiology is lacking for some of the pathogens and syndromes being described here. Third, I must acknowledge that change is constant – particularly in relation to antiretroviral drug development for HIV, resistance profiles of gonorrhea, and the ethical and legal climate surrounding the work – and that while general principles remain constant, some of the more specific

recommendations in this text may be quickly outdated as a result. Finally, I recognize that each of these chapter topics could be a book in itself, and I certainly cannot claim that any chapter is exhaustive on any topic. Rather, the goal of putting together this text was to provide a practical overview of issues relating to STIs in adolescents and young adults, in hopes that it will be useful for clinical providers from varying disciplinary backgrounds and levels of experience.

Atlanta, GA, USA Sophia A. Hussen

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Part III Major Pathogens

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Part I
Considerations in the Care of Sexually Active Adolescents

Chapter 1
Approach to the Sexual History and Physical Exam

Stephanie Addison-Holt and Meera Shah

Case Study
A 16-year-old female patient presented to her medical provider for a routine adolescent health exam. She was accompanied by her mother, as she had been during all previous medical visits. During the initial history-taking, the provider noticed that the patient appeared anxious. The provider took a general health history and then came to a part of the visit where she typically liked to speak with the teen alone. She explained confidentiality to the patient and her mother and then asked the patient's mother to step out of the room for the physical examination. Once her mother left the room, the patient revealed that she recently had her first sexual encounter and she was concerned that she might have a sexually transmitted disease. She denied any abdominal pain, vaginal discharge, or new rashes. She requested testing and further information about how to protect herself in future sexual encounters.

On physical examination, her vital signs were normal. Her physical exam was completely within normal limits, including normal heart and lung exams, no abdominal tenderness, and no genitourinary lesions or abnormal vaginal discharge.

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Questions

1. What are key elements of the approach to a sexual history in an adolescent or young adult?
2. What information should be obtained as a part of the sexual history?
3. What parts of the physical exam are most pertinent to assessing for risk of sexually transmitted diseases?

Adolescence is a unique developmental phase in which youth experience physical, psychological, and social changes as they approach adulthood. Physical changes during this time include a rapid and intense increase in height and weight (the "growth spurt") and the concomitant development of secondary sex characteristics due to hormonal changes. In addition to these physical changes, simultaneous psychological and social changes make this period of time one of constant changes. In the midst of these changes, youth are often vulnerable and may take part in risky sexual behavior. Adolescents and young adults aged 13–24 years are at increased risk for contracting sexually transmitted infections (STIs) relative to older adults, due to higher likelihood of having unprotected sex, having partners with higher rates of STIs, and having increased number of sexual partners [1]. Additionally, girls and young women are biologically more susceptible to certain STIs (e.g., gonorrhea and chlamydia) during adolescence due to physiological differences such as cervical ectopy (in which the more vulnerable columnar epithelial cells are present on the outside or vaginal portion of the cervix), which increase likelihood of STI acquisition at this age [2].

The Society for Adolescent Health and Medicine (SAHM), in an oft-cited position paper focused on the healthcare needs of adolescents, highlights the uniqueness of adolescence as a period in which the major causes of mortality and many of the causes of morbidity (e.g., pregnancy, sexually transmitted infections, and substance abuse) are potentially preventable [3]. Risky behaviors, including decisions about whether or not to partake in high-risk behaviors such as unprotected sex or drug and alcohol use, are often influenced by peer behaviors and norms [4]. The 2015 Youth Risk Behavior Survey, which is administered anonymously to a national sample of high school students, showed that 20.6% of sexually active teens had used drugs or alcohol at the time of their most recent sexual intercourse [5]. Additionally, 13.8% of those who were sexually active reported that they had not used any method of pregnancy prevention during last intercourse. The survey also showed that 41.2% of students had sexual intercourse and about 43% of those who were sexually active did not use a condom the last time they had sex [6]. Surprisingly, only 10.2% of all teens surveyed reported ever having been tested for HIV, in spite of national guidelines recommending universal testing and high rates of HIV among youth [5]. This large discrepancy between the numbers of sexually active teens and the amount who had been tested for HIV and/or used condoms further demonstrates the important

role that healthcare providers have to play in understanding and counseling teens regarding their sexual health. Healthy communication between providers and adolescent patients should also include a dialogue that emphasizes making healthy decisions regarding their sexual and reproductive health.

A critically important part of caring for adolescents is providing confidential care. Many adolescents are only willing to seek care for sexual or reproductive health concerns if confidentiality is guaranteed, preferably in an adolescent-friendly setting [7]. A 2013 study found that less than two thirds of adolescent patients and their physicians reported talked about dating or sex during an office visit [8]. Even when this conversation did occur, it lasted less than a minute on average. This low level of patient-provider communication around sex is not sufficient to provide adequate assessments, prevention counseling, or treatment for STIs [8]. Despite the staggering statistics about the burden of STIs in youth, multiple studies confirm these low rates of sexual health assessments by medical providers [9]. Some of the reasons for why healthcare providers may be less likely to complete a sexual history include restrictions on time, fear of offending the patient, perceptions that patients are low-risk, and discomfort with conducting the assessment [10]. Additionally, laws around confidentiality for sexually active minors vary from state to state, and practitioners may avoid sexual history questions for fear of not being able to provide confidential care in response [11]. In spite of these valid and reasonable concerns, providers must note that the consequences of missing or delaying identification and treatment of STIs can have long-term consequences. Not only does missing the diagnosis of a STI become a public health issue, but there are also negative medical outcomes for the individual patients, which can include infertility and mother-to-child transmission of different STIs [12]. Thus, it is vitally important to train our students, physicians, nurses, and public health practitioners who care for teenagers and young adults to strategically elicit a sexual history from adolescent patients with ease. This chapter will provide information about the importance of a sexual history, critical questions to ask regarding a patient regarding their sexual behaviors, appropriate physical exam techniques, and tips for counseling adolescents regarding sexual health.

Sexual History

General Approach

The general approach to obtaining a sexual history and performing a physical exam begins with assessing the adolescent's stage of cognitive and social-emotional development. The medical provider should be aware that of the three distinct stages of development, early, middle, and late adolescence, each stage is characterized by varying levels of abstract thought, reasoning ability, sense of identity, and relationships to peers and family (see Table 1.1) [13]. Providers should take care to ask questions in a nonjudgmental manner and take all needed steps to ensure confidentiality.

Table 1.1 Indicates developmentally tailored counseling for patients regarding their sexual health

	Adolescent stages and sexual health counseling		
Cognitive development	Social-emotional development	Counseling	Examples
Early adolescent (ages 11–14)			
Growing capacity for abstract thought Mostly interested in the present	Extremely self-conscious Tendency to return to "childish" behavior Greater interest in privacy	Ideal time for anticipatory guidance Sexual orientation/preference may be formed Provider needs to introduce sexual health topics and explore teen's definition of "sex." Younger teens not likely to bring up on their own Encourage patient to apply the same qualities of healthy friendships (mutual respect, communication) to romantic partners	It's important for me to discuss sexual health topics with all of my patients, maybe even before they have questions. What does the term "sex" mean to you? "Tell me about your best friend or what you look for in a friend… It sounds like you would not want to hang out with someone who treated you badly or made you feel badly about yourself"
Middle adolescence (ages 15–17)			
Greater capacity for setting goals Continued growth of abstract thought	Intense self-involvement Increased drive for independence Greater reliance on friends	Discussion of peer group may help teen talk more freely and reveal misconceptions about sex and contraception Ask what is most important to them about birth control (e.g., that it works really well or does not make them gain weight) Support them to make the decision based on counseling	"What are your friends using for birth control? What do they say about it?" "Have your friends or family talked about any birth control methods? What are your thoughts about them?" It sounds like the most important thing for you to avoid pregnancy and you said pills are hard to take. What do you think would be the best method for you?
Late adolescence (ages 18–21)			
Greater ability to delay gratification and plan for future Can reason through problems	Increased sense of identity and emotional stability Desire for intimacy and serious relationships	Ask about future plans. Discuss how having a child now might affect these plans Ask what partner thinks about childbearing and birth control Discuss that with a long-term, serious sexual relationship comes a higher chance of pregnancy and, if pregnancy not desired, a greater need for effective birth control	Do you want to have children in the future and, if so, when? It sounds like you do not want to have a child now. What birth control method would work best for you?

The HEEADSSS interview method of obtaining psychosocial history can be used when interviewing teens as a way to capture all of the essential information needed for a complete adolescent visit. HEEADSSS is an acronym for the major topics that should be covered: Home, Education, Employment, Eating, Activities, Drugs, Sexuality, Suicide and Safety [14]. Although a provider may have a specific order into which she/he likes to ask questions, the preferred style is one that is conversational in nature and patient-led (while still including, at the very least, the major domains outlined in the HEEADSSS acronym). Before this section of the visit begins, the adolescent should be informed that the sexual history is a normal part of their visit and reassured that questions related to sex are asked of *every* teen [13].

Providers may be relieved to know that many adolescents actually prefer when their provider asks questions about their sexual health, as they often may have questions they are too embarrassed to ask elsewhere [14]. One study found that the best way to obtain timely and honest information (as long as privacy could be maintained) about sexual behavior was to administer a pre-visit questionnaire including sexual health items. This survey could be administered either in a digital format or paper survey and could be completed in the waiting area or exam room prior to seeing the provider [15]. Obtaining this information prior to the visit gives the provider a snapshot of the patient's sexual health history and allows the provider to focus on areas that may need more attention. Additionally, these surveys may help youth who are embarrassed about their sexual behavior or preferences to disclose to their physicians more easily. It is also important to note that healthcare providers can build rapport with the adolescent by asking general health-related questions before getting to more sensitive questions about sexual health.

Providers should avoid making any assumptions regarding their patient's partner preference, sexual orientation, or sexual behaviors. Making incorrect assumptions may jeopardize the relationship between the provider and teen and can create gaps in understanding, discomfort, or lack of trust. Providers should also aim to be gender-neutral and objective in their history-taking (Table 1.2) [15]. By remaining gender-neutral and objective, providers can demonstrate that they are obtaining information to help patients, not to judge them. Asking open-ended questions is an important way to minimize discomfort and increase participation by the teen in the conversation. Additionally, the healthcare provider must recognize that gender identity, sexual orientation, and sexual behaviors are not synonymous. Gender identity is defined as one's internal sense of being a man, woman, or other gender, whereas sexual orientation describes a person's sexual and romantic attractions [16]. The

Table 1.2 Demonstrates examples of ways to ask a sexual history without assuming partner gender or sexual identity

Heterosexist question	Instead ask
Do you have a girlfriend?	Are you dating anybody?
What do you and your boyfriend do together?	What do the two of you do together? Tell me about your partner?
Are you and your girlfriend sexually active?	Are you having sex? Are the two of you in a sexual relationship?

patient should be asked what, if any, gender they identify with, who they are attracted to, and what specific sexual behaviors they have engaged in [16].

Parental Involvement in the Visit

It should be standard practice in every adolescent health visit for the provider to ask accompanying parent(s)/guardian(s) to leave the room for at least part of the visit. Providers can mention this at the beginning of the visit, sharing with both parents/guardians and teens that teens are always given time alone with their medical provider at every adolescent visit. Reasons behind this practice, which can be communicated to parents/guardians, include helping teens work on independence, taking charge of their own health, and learning to communicate with their provider directly about potentially sensitive topics. If parents/guardians are resistant to leaving the room, clarifying their concerns and providing reassurance of the limits of confidentiality (e.g., suicide, physical/sexual abuse) are generally useful for helping parents/guardians to understand that they will be notified if the provider feels that their teen is unsafe or in danger. Sometimes an adolescent or parent may report that they have a good relationship and the parent does not need to leave – in these instances, the provider should focus on the importance of independent skills-building. One of the particular nuances that may be underestimated by providers is that even in the most open teen-parent relationships, the teens are less likely to disclose the *timing* of specific sexual events, which is often very key in obtaining a thorough history. For example, a teen who just had a sexual encounter yesterday may not ready disclose that particular information if they were supposed to be participating in a school-related activity that day. Of note, however, there are also advantages to having parents present for other parts of the visit. If a provider is seeing an adolescent in a clinical setting with their parent present, they have the opportunity to learn what sexual health education is discussed at home and can gain insight into family attitudes toward adolescent sexual health. This is important because conversations between teens and parents are important predictors of their sexual health behaviors [17]. It is important that providers are careful not to make the parent or guardian feel isolated and encourage them to serve as an ally and advocate in maintaining their child's health (including their sexual health).

Critical Questions to Ask

If a patient endorses sexual activity and/or specific sexual health concerns, it is important to screen the patient for high-risk behaviors. Providers should ask about the gender of their partners, how many partners they have had, what kind of sex (e.g., oral, anal, vaginal) they are having, and any risk factors for sexually transmitted infections or pregnancy (e.g., drug and alcohol use with sex).

Subsequently it is important to counsel all youth about safe sexual practices, preventative behaviors, and resources. Providers can conclude this portion of the visit with an invitation to continue to communicate about their sexual concerns at future appointments.

If a patient denies any particular sexual concerns, it is important to ask if they have ever had sex. Even for patients who do not report sexual activity, medical visits provide an excellent opportunity to counsel on safe sexual behaviors and resources for the future (when the patient does consider becoming sexually active). It is also a chance to assess potential for future sexual behaviors, based in part on peer behaviors and current alcohol or drug use.

When obtaining a sexual history, it is important to be very specific when defining sexual behaviors, as definitions may vary among teenagers. It may be prudent to ask what a patient's definition of sex is and then ask more specifically how they describe or understand other sexual behaviors. Importantly, oral and anal sex may not fall into their usual definition of "sex," or teens may find these behaviors acceptable because they are perceived to be lower-risk [18]. For younger adolescents, or any youth for whom there is still some difficulty assessing sexual behaviors, asking general questions about exposure to and/or touching of private body parts may be helpful.

The Centers for Disease Control and Prevention (CDC) has developed a guide to asking the sexual history which assists providers in assessing risk of sexually transmitted illnesses and offer risk reduction counseling and STI testing and treatment [19]. The five "P"s of sexual health stand for *p*artners, *p*ractices, *p*rotection from STIs, *p*ast history of STIs, and *p*revention of unwanted pregnancy (see Table 1.3).

Table 1.3 Outlines the 5P's: Framework for asking sexual health and history questions

The 5 Ps	Important questions to ask
Partners	The number of partners in the past 12 months The gender of their partners The specifics of their relationship (length, open relationship vs. monogamous) Condom use with their partners Partner's risk factors for STDs Age of partners Sexual and physical abuse by partners
Practices	Ask about specific sexual contact Ask about oral, vaginal, and/or anal sex while giving definition of each Drug or alcohol use before or during sex Ask about exchanging sex for money or drugs
Protection from STDs	Condom use including type and frequency
Past history of STDs	Ask if patient and partner have ever been diagnosed with STD Ask if patient and partner have any symptoms of STDs Ask if patient or partner has ever been tested or treated for STDs
Prevention of pregnancy	Assess pregnancy intention by asking if they are trying to conceive Ask if patient is concerned about getting pregnant or getting partner pregnant Ask about methods of pregnancy prevention

Given that these are only basic areas of STI assessment, some patients may require more detailed history given certain special circumstances; however, this framework can serve as a useful starting point.

Physical Exam

The physical exam of an adolescent plays an important role in assessing risk for STIs. The most important areas of examination include overall physical assessment, oral, abdominal, genitourinary, rectal, lymph, and skin exams. Each STI has its own set of physical findings that is discussed in greater detail elsewhere in the book. When performing a physical exam, one should look for obvious signs of systemic illness that include weakness or weight loss, which could be a sign of HIV infection. An oral exam to look for ulcers, sores, and inflamed or purulent oropharynx might indicate infection with herpes simplex virus or *Neisseria gonorrhoeae.* The abdominal exam should include visual inspection, assessing for liver tenderness or enlargement, lower abdominal tenderness, rebound tenderness and guarding, and flank tenderness (e.g., pelvic inflammatory disease). The female genitourinary exam should include visual inspection for obvious lesions that may include ulcers, warts, pustules, vesicles, swollen labia, clitoral swelling, inguinal lymphadenopathy, and/or vaginal discharge. If a patient has a genitourinary complaint that includes profuse vaginal discharge, vaginal bleeding of unknown etiology, lower abdominal pain, or rebound tenderness not easily explained by other parts of history and exam, a speculum exam to assess for cervical lesions, bleeding, or other abnormalities should be included. A male genitourinary exam may or may not reveal mucoid or purulent urethral discharge, testicular swelling, meatal swelling, erythema, or inguinal lymphadenopathy. A visual examination of the rectal area is also warranted to assess for lesions, discharge, and/or bleeding. A thorough skin exam may demonstrate rashes seen in a variety of sexually transmitted diseases (e.g., syphilis) [18].

Case Study Follow-Up
The patient is an adolescent who is concerned that she may have a sexually transmitted disease. She does not have signs and symptoms typical of STIs. In this case it is important to explain confidentiality to the teen, remove judgment and assumptions, and ask open-ended questions regarding her sexual experiences and health. It is important to incorporate the 5Ps and to also perform a thorough physical exam looking for any abnormal findings. The screening tests that are obtained should be relayed to the patient. A discussion on prevention and staying healthy should also be included.

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Chapter 2
Care of Sexual and Gender Minority Adolescents

Maureen D. Connolly and Nadia Dowshen

Case Study
A 19-year-old transgender woman comes into a teen health clinic requesting sexually transmitted infection (STI) testing. She has no symptoms. She is sexually active with men only and has a boyfriend. She currently has no other partners but reports that she used to exchange sex for money with partners she met online, which she stopped a few months ago. She states she does not use condoms with her partner but uses condoms 100% of the time if she is working (i.e., engaging in transactional sex), except for oral sex. She was last tested for human immunodeficiency virus (HIV) at a community event 6 months ago and reports the result was negative. She has never been tested for other STIs. She has no allergies and is not currently taking medications, but reports being on estradiol injections in the past, which she purchased online. She is interested in starting hormones that are prescribed by a doctor. She also reports having bilateral silicone buttock injections last year, which were performed at a gathering at a local motel. She reports no other surgeries.

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On physical examination, vitals are within normal range and she is well-appearing. There is mild bilateral tonsillar erythema with scant purulent exudate. She has bilateral Tanner II breast development. Skin exam is normal, and sites of previous buttock injections are well-healed.

Questions

1. What are some steps that can be taken to help this patient feel comfortable during the visit?
2. What STI testing is indicated today?
3. What other health concerns should be addressed at today's visit?

Given that approximately 11% of adolescents in the United States identify as a sexual or gender minority (SGM, i.e., lesbian, gay, bisexual, transgender, questioning/queer), pediatricians, internists, and family practitioners are likely to care for SGM patients during their career. Studies have shown that SGM youth (SGMY) are at risk for poor health outcomes, especially in regard to sexual health [1]. These health risks are not due to a young person's sexual orientation or gender identity per se, but instead the result of stress, stigma, and isolation they may face as the result of their SGM status. In the face of such adversity, however, many SGMY have developed personal tools for resilience, and it is important to take a strengths-based approach to caring for them. By providing accurate information and support in a nonjudgmental manner, healthcare providers can have a positive impact on the sexual health and overall well-being of SGMY.

Definitions and Epidemiology

Sexual orientation refers to an individual's physical and emotional attractions to others. While sexual orientation has traditionally been described as *homosexual*, *heterosexual*, or *bisexual*, many young people are more comfortable with newer terminology like *queer*, *questioning*, or *pansexual* to convey that their sexual orientation exists outside of conventional categories that rely on a binary system of gender identity. Importantly, the term *queer*, which has grown in usage among young people, has been reclaimed from its previously derogatory connotations to reflect any identity that expands beyond traditional heterosexual societal norms [2].

Gender identity is a personal and culturally defined construct that refers to one's innermost sense of being male, female, a combination of both, or neither. *Transgender* and *trans** are umbrella terms used to describe those whose internal gender identity does not match their assigned sex at birth. This includes those whose gender identity aligns with what is typically associated with the opposite sex (i.e., an individual who was assigned male at birth but who identifies as a girl or woman).

These umbrella terms also include those whose identity is somewhere between boy/man and girl/woman or whose identity falls outside of a gender binary in which boy/man and girl/woman are the only categories [3]. These individuals may refer to themselves as *gender nonconforming*, *genderqueer*, *gender fluid*, *gender creative*, *gender independent*, or *gender nonbinary* [4]. *Cisgender* refers to those whose assigned sex at birth aligns with their gender identity.

Data from the 2015 Youth Risk Behavior Survey (YRBS) show that nationally, 88.8% of high school students (in grades 9–12) identified as heterosexual, 2.0% identified as gay or lesbian, 6.0% identified as bisexual, and 3.2% were not sure of their sexual identity [1]. In the United States, the majority of population-based health risk assessments do not address gender identity [5]; however, a regional version of the YRBS was administered to middle school students in San Francisco in 2011, which also included the question "What is your gender?" with possible responses including "male," "female," and "transgender." Results from this random sample of 2730 youth in grades 6–8 showed that 1.3% of middle school students identified as transgender [6]. Survey results from a nationally representative sample of 8166 high school students in New Zealand demonstrated that 1.2% reported being transgender and 2.5% reported being not sure about their gender [7].

SGMY have elevated risk for poor health outcomes related to sexual health and are at increased risk for violence and victimization. Compared with heterosexual youth, sexual minority youth are more likely to have experienced sexual dating violence, to be sexually active, to have earlier sexual debut (before age 13), to have had four or more sexual partners, and to have not used a condom during last sexual intercourse [1]. Compared to cisgender peers, gender minority youth are more likely to be afraid that someone at school will hurt them, to be bullied at school at least weekly, and to have been hit or physically harmed by another person [7].

Approach to Sexual Healthcare with Sexual and Gender Minority Youth

Creating a Welcoming Environment

Given these disparities, inclusive and affirming sexual health services for SGMY are essential to ensure their well-being. Unfortunately, many young people have had negative experiences in clinical settings, which may make it less likely for them to seek care [8, 9]. With the stigma and prejudice that exist broadly in the world and more specifically in clinical settings, it is important to take proactive steps to let SGMY know they are welcome and their identities will be respected. Upon entering a healthcare facility, many SGMY will search for clues that the space is one in which they will be safe and supported. Having posters, brochures, and reading materials that include depictions of SGM people and families can convey that a healthcare organization recognizes and serves the SGM community. It should be clearly posted that patients can use the bathroom that most fits their gender identity

and, if possible, there should be an all-genders, single-stall bathroom for those who do not feel comfortable in public restrooms. The registration process is a key indicator for young people about the nature of the clinic environment, and processes and forms should be reviewed to ensure they acknowledge and affirm different gender identities and sexual orientations. All staff, especially those with direct patient contact, should receive training on SGM identities, terminology, and health disparities, as well as how to avoid stereotypes and assumptions about a patient's sexual orientation and/or gender identity [10] (Figs. 2.1 and 2.2).

Fig. 2.1 Example of clinic poster that conveys a welcoming clinical environment to SGMY

Fig. 2.2 Example of clinic poster that conveys a welcoming clinical environment to SGMY

Transgender and gender-nonconforming patients face particular challenges when trying to access healthcare, especially when seeking gender-affirming medical therapy. The National Transgender Discrimination Survey showed that 19% of adults were refused care due to their transgender or gender-nonconforming identity and 28% of respondents were subjected to harassment in medical settings [11]. There are ample opportunities through organizations like the World Professional Association for Transgender Health (WPATH) [12], the University of California San Francisco (UCSF) Center of Excellence for Transgender Health [13], the National LGBT Health Education Center [14], and the Endocrine Society Guidelines [15] to learn about providing care to transgender youth, including gender-affirming hormone therapy. However, if a clinician is not able to provide hormone therapy, it is important to be knowledgeable about referral options for patients who wish to pursue medical or surgical transition. Additionally, offering information to patients regarding local support groups, the process for legal name and gender marker change, and resources for transition at school will provide support for transgender youth as they navigate the numerous challenges that can arise as the result of their gender minority status.

Setting the Stage for Confidentiality, Nonjudgment, and Honesty

Confidentiality is an essential aspect of working with young people and should be emphasized at every step in the clinic visit, from the front desk to the exam room. In addition to explaining that their information will be kept private, providers should be clear with patients about the limits of confidentiality and should familiarize

themselves with state policies regarding minor rights for confidential services. Detailed information regarding individual state policies can be found at the Guttmacher Institute [16] (https://www.guttmacher.org/united-states/teens/state-policies-teens). Every visit with an adolescent should include talking with the patient alone, without parents/family in the room. Discussing issues of sexual identity and gender identity should first be done with the patient alone and only shared with family when the patient has given permission. When asking about highly personal information, it is helpful to remind youth that the clinic is a "judgment-free zone" where they will always be treated with respect. Young people should understand that they will hear honest and accurate information from their provider and they should feel empowered to make decisions about their own health.

Taking a Sexual History

After setting the stage, the provider should proceed with an established set of open-ended, inclusive questions. By using the same approach for each patient, providers can avoid making incorrect assumptions about a patient's relationships and sexual health, regardless of their identity. The five Ps (*partners*, *practices*, *past history*, *protection*, *pregnancy*) are a helpful mnemonic from the CDC's *A Guide to Taking a Sexual History* [17], which have been adapted by the authors to also include *positivity* and *pleasure*. While providers may not have enough time in a short clinical encounter to address each of these issues in depth at every visit, these seven concepts provide a practical starting point for taking a comprehensive sexual history and can be further explored at subsequent visits:

1. Positivity: It is important to approach the sexual history from a place of positivity. Romantic attraction and sex are common elements of the human experience, yet talking about sex can be awkward or embarrassing, regardless of a patient's age. Teens receive many external messages about who they should or should not be attracted to and the right or wrong way to have to sex. The goal during taking a sexual history is to create a space for patients to express their feelings about sexual health and relationships and to explore the choices that feel right for them and will help them stay healthy. Regardless of what providers think patients "should" be doing, positive feedback and affirmation should be emphasized. For example, when patients share that they are using condoms 20% of the time, often an initial reaction is focused on the 80% of the time when condoms aren't being used. An alternative approach would be to first offer praise for using condoms at all and to celebrate the effort they are making to stay healthy before exploring ways they feel they could increase their condom use. Another example might be prefacing questions about sexual practices with a statement such as "There are lots of good ways that people have sex which each other" as a way to offset cultural stigma related to what is "normal" or "not normal." By approaching the sexual history with positivity and affirmation, the goal is to have patients walk away feeling empowered about a topic that is often accompanied by discomfort and shame.

2. Partners: Providers should never assume the gender of a young person's partners. Questions such as "Who are you attracted to?" or "Who do you see yourself being with?" are open-ended ways to better understand patients' romantic relationships and attractions. By asking about partners instead of identity, patients are given the space to describe their partners without being asked to identify as "gay," "straight," or "bisexual," terms that can be limiting and may not capture how young people see themselves. Further, as young people develop and understand their gender identity, partners may include people who are gender nonconforming or gender nonbinary. The traditional approach of defining partners in terms of "men, women, or both" reinforces a binary that may not fully capture the gender identity of a patient or their partners.
3. Practices: It is important to remember that sexual identity and sexual behavior are not synonymous and providers should not make assumptions about the ways a patient is having sex, even if the patient has disclosed an SGM identity. Open-ended questions should be used, such as "How do you have sex? What body parts do you and your partners use to have sex? Who does what?" This may initially be met with confusion on the part of an adolescent patient but can be clarified by asking questions such as "Do you have vaginal sex? Oral sex? Anal sex? Do you top, bottom, or both? Do you use strap-ons or toys?" Resistance or embarrassment can typically be overcome by approaching the questions with a positive, matter-of-fact attitude which conveys that sex is a normal part of life and an important topic to discuss in healthcare settings.

   This is also a chance to explore other factors related to a young person's sexual health. Providers should inquire about whether a patient has been forced to have sex or is exchanging sex for money, drugs, or a place to stay. They should ask if a patient is only able to have sex when they are high or drunk and to explore why that might be. If a patient watches pornography, it is important to inquire about how often and for how long and to explore whether or not it is having an impact on their real-world relationships and responsibilities.
4. Past history: It is helpful to ask if a patient has ever been tested for or diagnosed with an STI. If a patient has been tested previously, it is an opportunity for positive feedback, as getting tested can be intimidating and is often be accompanied by anxiety. Additionally, patients may have been told of a positive result but never received treatment. Finally, if a patient has had one or multiple prior STIs, they may be a good candidate for pre-exposure prophylaxis (PrEP) for HIV. Regardless of the number of partners a patient has had, STI and HIV testing should always be offered as a routine part of medical care.
5. Protection from STIs: It is important to ask what patients are doing to protect themselves from STIs. This includes condoms but can also include things like using lube for anal sex; using gloves, dental dams, or sex toys; starting PrEP; reducing the number of sexual partners; or reducing substance use that may be associated with unprotected sex. Providers should take a harm reduction approach when discussing a menu of practical strategies for STI prevention. This includes respecting each patient's unique history and preferences when developing a plan for risk reduction. Instead of asking the patient to align with a prescribed approach that comes from the provider, the emphasis should be on supporting

patients as they take steps to decrease STI risk in a way that makes sense for their individual life circumstances.

6. Pregnancy plans: Providers should never make assumptions about a patient's pregnancy plans or fertility concerns but should instead explore current feelings about having children and hopes for the future in regard to having a family. Regardless of a patient's sexual orientation or gender identity, family planning options should always be discussed, including contraception, childbearing options, and fertility preservation. This is especially true for transgender youth who are interested in starting gender-affirming hormone therapy, which can affect sexual function and fertility.
7. Pleasure: The notion of pleasure is often overlooked when working with adolescents but is an important part of a sexual health history, which should go beyond merely talking about the risks of STIs, HIV, and pregnancy. By asking questions such as "Do you enjoy sex? Do you have sex because you want to? Do you want to have sex more or less than your partner does?" providers have an opportunity to discuss power dynamics, issues of consent, and healthy relationships.

Physical Examination

When initiating the physical exam with SGMY, as with all youth, it is important to explain what will be done beforehand and to give the patient full control to stop the exam at any time. Because sexual minority individuals are more likely to have experienced physical and sexual abuse [18], it is important to take a trauma-informed approach by being mindful of the impact of past traumas, addressing the ways that trauma may emerge over the course of an exam, and actively working to avoid retraumatization. The genital exam is not always necessary on the first visit and can often be left until a trusting therapeutic relationship has developed. Transgender and gender-nonconforming youth may have particularly intense distress at the prospect of a breast or genital exam due to feeling like they don't identify with their natal anatomy (i.e., examining the breast tissue of a patient who was assigned female at birth but identifies as a boy). Regardless of a patient's gender identity, physical examination for cancer screening should be dictated by the anatomy of the patient and not the patient's gender identity [19].

Sexual Health Considerations in Sexual and Gender Minority Youth

Human Immunodeficiency Virus

Gay, bisexual, and other men who have sex with men (collectively referred to as MSM) made up an estimated 2% of the population but 55% of people living with HIV in the United States in 2013 [20]. Rates of new infection are increasing among adolescents and young adults, and in 2014, gay and bisexual men aged 13–24

accounted for an estimated 92% of new HIV diagnoses among all men in their age group and 27% of new diagnoses among all gay and bisexual men [21]. A systematic review of studies from 15 countries estimated that HIV prevalence among transgender women was nearly 50 times as high as that of other adults [22]. Communities of color are disproportionately affected by the epidemic, and if current diagnosis rates continue, one in two Black/African American gay and bisexual men and one in four Latino/Hispanic gay and bisexual men will be diagnosed with HIV in their lifetime [23].

It is important to recognize that these racial differences are not due to increased risk behavior on the part of individuals within these racial/ethnic groups [24] but instead reflect structural inequities that result in increased segregation and decreased access to healthcare in communities of color [25, 26]. While these statistics are sobering and represent a call to action for providers who care for adolescents and young adults (AYA), it is also important to remember that the health and wellness of young men who have sex with men (YMSM) and young transgender women (YTW) involve much more than the prevention or treatment of HIV and should therefore never be the sole focus of a clinical encounter. By engaging with patients around health issues that are most important to them, such as gender-affirming hormones, providers are able to build therapeutic relationships over time that allow for meaningful conversations about safe sex and healthy relationships.

Providers working with adolescents and young adults should have an understanding of nonoccupational post-exposure prophylaxis (nPEP) and pre-exposure prophylaxis (PrEP) for HIV. Youth who have had condomless insertive or receptive anal or vaginal intercourse with a partner who is known to be HIV-positive or those who have experienced a sexual assault should be offered nPEP, in addition to other STI testing and treatment. Situations in which a young person reports a consensual sexual encounter with a partner whose HIV status is unknown should be approached on a case-by-case basis, taking into account local HIV prevalence rates and the type of sexual activity (i.e., receptive anal intercourse carries a higher transmission rate than receptive vaginal intercourse [27]). It is important that providers and young people know that nPEP is most effective when initiated as soon as possible after HIV exposure and is unlikely to be effective when started more than 72 hours after exposure [27]. The preferred regimen for adults and adolescents aged 13 and older with normal renal function is a 28-day course of a three-drug regimen consisting of tenofovir 300 mg/emtricitabine 200 mg (TDF/FTC or Truvada) once daily and either raltegravir 400 mg (Isentress) twice daily *or* dolutegravir 50 mg (Tivicay) once daily [27]. For those who have repeated high risk of exposures, a 28-day course of nPEP can be transitioned to ongoing PrEP. Detailed guidelines for the prescription of nPEP can be found at https://www.cdc.gov/hiv/risk/pep/index.html.

For young people who are at ongoing risk for contracting HIV, PrEP is an important addition to the menu of options for HIV prevention that can be discussed with patients. As of 2020, TDF/FTC (Truvada) and TAF/FTC (Descovy) are the only medications FDA-approved for use as PrEP and are taken once daily, although alternative formulations, such as injections and implants, are in development. Young MSM and transgender women are key target populations for PrEP. Men or transgender women who have male sex partners, have had anal sex without condoms, have

had any STI in the past 6 months, or are in an ongoing sexual relationship with an HIV-positive male partner are good candidates for PrEP. However, PrEP should be discussed with anyone who is at substantial risk for HIV infection, including patients with a history of multiple STIs, injection drug use, or transactional sex [28]. Detailed guidelines for use of PrEP can be found at https://www.cdc.gov/hiv/clinicians/prevention/prep.html.

In 2018, the FDA approved TDF/FTC (Truvada) for us as PrEP in adolescents weighing more than 35 kg (77 lbs) [29]. In the first US study of TDF/FTC as PrEP among adolescent MSM ages 15–17 [30] and the companion study of 18–22-year-old MSM [31], the majority of participants achieved protective drug levels during monthly visits, yet adherence decreased with quarterly visits. While CDC guidelines recommend follow-up visits every 3 months, these studies suggest that providers working with adolescents and young adults may need to consider more frequent follow-ups to better support adherence. Emerging data regarding the safety of TDF/FTC in this population support short-term renal safety but do show a decline in bond mineral density (BMD), the clinical significance of which is yet to be determined [32]. Discussion of risks and benefits should include the fact that HIV itself causes clinically significant bone health problems.

Finally, it is essential to be aware of state laws regarding confidentiality related to PrEP. Some young people may not feel comfortable with seeking parental consent due to not wanting parents to know they are sexually active or making assumptions about their sexual orientation. While no state expressly prohibits minors' access to PrEP and all states allow some minors to consent to medical care for the diagnosis or treatment of STIs, only eight allow minor consent to preventive or prophylactic services [33]. Even if providers are unable to prescribe PrEP due to concerns regarding confidentiality or cost, it is important to include a discussion of PrEP and nPEP during anticipatory guidance conversations, especially with SGMY (similar to anticipatory guidance about contraception and emergency contraception). Increasing knowledge about these HIV prevention tools is an important step toward curbing the epidemic among adolescents and young adults.

Chlamydial and Gonococcal Infections

Chlamydia trachomatis and *Neisseria gonorrhoeae* are bacterial STIs that are highly prevalent among young people. Young women who have female partners are at substantial risk for chlamydia infection, and in one study, it was demonstrated that *Chlamydia trachomatis* infection was higher in women who reported any sexual activity with other women (7.1%), compared to women who were only sexually active with men (5.3%) [34]. MSM and transgender women are at increased risk for gonorrhea and chlamydia, including rectal and pharyngeal infections. In a study of over 20,000 MSM from 42 STI clinics in the United States, rates of chlamydia were reported at 8.4% for urogenital infection, 2.9% for pharyngeal infection, and 14.1%

for rectal infection, while rates of gonorrhea were reported at 1.1% for urogenital infection, 7.9% for pharyngeal infection, and 10.2% for rectal infection [35].

The CDC recommends routine annual screening for chlamydia and gonorrhea for all sexually active women less than 25 years of age, regardless of sex of partners. The CDC also recommends that MSM be screened for gonorrhea and chlamydia at least annually at sites of contact (urethra, rectum, pharynx) regardless of condom use and every 3–6 months if at increased risk [36]. It is important to note that in the above study, more than 85% of extragenital chlamydia and 70% of extragenital gonorrhea infections were associated with negative urethral tests at the same visit and would not have been detected with urine screening alone [35]. Therefore, it is essential to do three-site collection whenever performing STI testing for young MSM or transgender women. Providers working with SGMY should be aware of how to correctly send rectal and pharyngeal samples. This may involve calling the laboratory to verify the type of tube that should be sent and correct labeling of the site of collection. Pharyngeal samples are collected by swabbing the bilateral tonsils, posterior wall, and uvula. The rectal sample is collected by inserting swab 1 inch into the anus and gently turning to make contact with rectal wall for 5–10 seconds (Figs. 2.3 and 2.4).

Rectal chlamydia and gonorrhea are often asymptomatic but can also cause proctitis, symptoms of which include diarrhea, rectal pain or bleeding, tenesmus, and rectal discharge. Recognizing and treating proctitis is imperative because it can be associated with an increased risk of HIV infection [37]. When evaluating MSM or

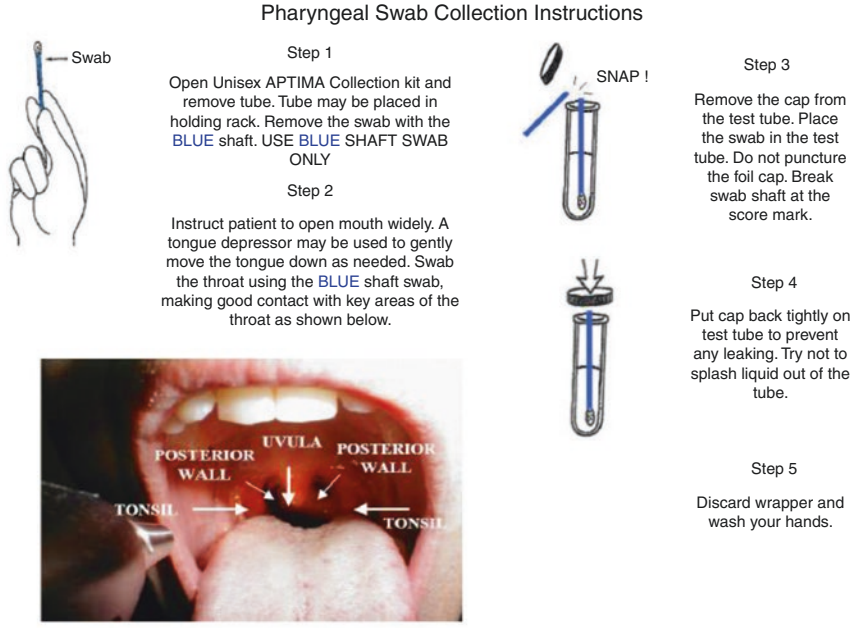

Fig. 2.3 Pharyngeal swab collection

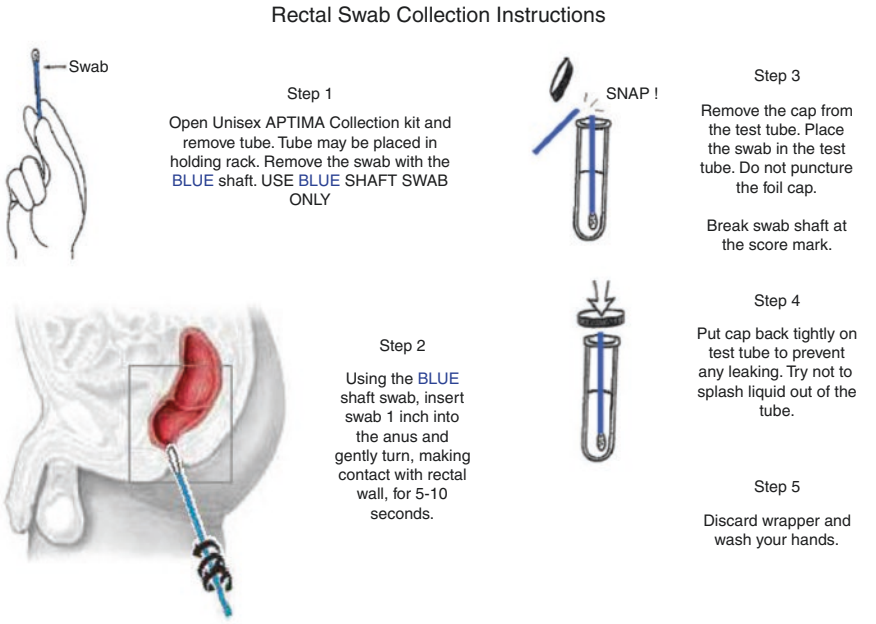

Fig. 2.4 Rectal swab collection

transgender women with rectal symptoms, it is also important to consider lymphogranuloma venereum (LGV), which is caused by *C. trachomatous* serovars L1-L3 and can cause symptoms of proctocolitis, often mimicking inflammatory bowel disease. LGV can be an invasive, systemic infection, and if it is not treated early, LGV proctocolitis can lead to chronic colorectal fistulas and strictures. It is possible to differentiate LGV from non-LGV *C. trachomatis* via PCR-based genotyping; however, this testing is not widely available, and results are not typically available in a timeframe that would be relevant to clinical management [36]. Therefore, patients who are diagnosed and treated for rectal chlamydia with 1000 mg oral azithromycin but have persistent GI symptoms may warrant empiric treatment for LGV with doxycycline 100 mg orally twice a day for 21 days [36].

Syphilis

Data show rates of syphilis are increasing at an alarming rate, with a 19% increase in 2015 [38]. While rates have increased among both men and women, men account for more than 90% of all primary and secondary syphilis cases. MSM account for 82% of male cases where the sex of the sex partner is known [38]. Syphilis rates continue to rise among young MSM, with steadily increasing rates among 15–19-year-old MSM from 2006 to 2015 [38]. The CDC recommends annual syphilis testing for MSM and every 3–6-month screening for those at increased risk [36].

Hepatitis

Hepatitis A (HAV) is a self-limited disease that typically presents with fever, jaundice, nausea, and stomach upset and is typically treated with supportive care. It is transmitted via the fecal-oral route and may therefore be more prevalent in young people who engage in oral-anal sexual contact [19]. Hepatitis B virus (HBV) can be transmitted through blood or sexual contact and can lead to either acute or chronic infection. While routine immunization in infancy has led to a largely immune adolescent population, immunity can wane over time. It is important to screen for hepatitis B infection (hepatitis B surface antigen and core antigen) and immunity (hepatitis B surface antibody) prior to initiation of PrEP. This is due to the fact that both tenofovir and emtricitabine (the components of Truvada) are also active against hepatitis B infection and if patients with active HBV infection stop taking PrEP, reactivated HBV infection can result in hepatic damage [28]. Although hepatitis C virus is less common among adolescents, young people living with HIV should be screened for HCV yearly [36]. Additionally, patients who report a history of injection drug use, tattoos, or silicone injections performed in unregulated settings or hormone injections not prescribed by a doctor should also be screened for HCV.

HPV

Human papillomavirus (HPV) is the most common sexually transmitted infection in the United States [38], with HPV 6 and 11 responsible for approximately 90% of genital warts [39] and HPV 16 and 18 responsible for approximately 70% of cervical cancers worldwide [40]. The 9-valent HPV vaccine is recommended for all adolescents up to age 21; the recommended upper age extends to 26 for women and MSM for those who have not previously been vaccinated [41]. HPV is commonly detected among WSW and therefore should be screened for cervical cancer according to population guidelines [42]. Transgender men who have not undergone hysterectomy should also be screened for cervical cancer according to population guidelines [13]. There is insufficient evidence to recommend routine anal cytology for YMSM and transgender women to assess for dysplasia, although some practices will perform yearly anal cytology for those living with HIV [43].

Bacterial Vaginosis

Bacterial vaginosis (BV) is a common cause of vaginal discharge in women of reproductive age, with national prevalence estimates ranging from 10% to 40% [44]. Although few studies have focused on WSW, BV appears to be highly prevalent in this population with prevalence rates ranging from 25% to 50% [45–47].

While sexual transmission of BV has not been established, among WSW it is associated with an increased number of female sexual partners, receptive oral sex, and a female partner with BV symptoms [48–50]. One randomized controlled trial in WSW demonstrated that reducing transmission of vaginal fluid through gloves and condom use for sex toys did not reduce recurrence [51].

Use of Toys

Use of sex toys such as vibrators, cock rings, butt plugs, and strap-ons is common among people of all sexual orientations and gender identities. It is helpful to normalize the use of toys which, in addition to adding pleasure to young people's sexual lives, can represent a risk reduction strategy for those at high risk for acquiring STIs/HIV [52]. Vibrators and strap-ons can be covered with a condom before use to avoid contact with bodily fluids. After use with one partner, the condom should be changed before coming into contact with another partner. Most toys come with instructions for cleaning and care, but using soap and water is generally effective, followed by air-drying [53]. Patients should be reminded to read instructions carefully, as many toys cannot be placed in the dishwashers and may need to have batteries removed before cleaning.

Contraception and Family Planning

Discussion of family planning intentions is an important aspect of caring for SGMY. Providers should never make assumptions about a patient's desire for pregnancy or fertility, now or in the future. Asking about reproductive goals allows providers a chance to better understand a patient's vision for their future and family structure. A young person who is currently with a same-sex partner(s) may have had opposite sex partners in the past and may again in the future, and therefore an exploration of contraceptive options is always warranted if a patient states they are not ready to be a parent. For youth living with HIV, family planning conversations offer a chance to discuss PrEP for serodiscordant partners [19]. For SGMY with only same-sex partners, childbearing options include assisted reproductive technologies, surrogacy, and adoption. For transgender youth who are considering gender-affirming hormone therapy, it is important to understand fertility preservation options, including oocyte preservation and sperm banking. Alternatively, it is important for youth to understand that gender-affirming hormones are not intended to be used as contraception and that it is possible for fertility to persist while on masculinizing or feminizing hormone therapy.

Case Discussion

The patient was able to indicate affirmed name, gender identity, and assigned sex at birth on the health center's intake form, which allowed the health center staff to use the correct name and pronouns throughout the visit. Comprehensive STI testing was performed, including gonorrhea/chlamydia with urine, rectal, and pharyngeal samples, as well as serum RPR and fourth-generation HIV testing. After discussion of HIV prevention strategies, the patient stated she was interested in starting PrEP, so creatinine, hepatitis C antibody, hepatitis B surface antigen, antibody, and core antibody were also sent. The patient was very interested in starting feminizing hormones with the help of a doctor, and she was referred to a colleague who provides gender-affirming hormone therapy. The importance of having procedures such as silicone injections performed in a medical setting by a trained provider was also discussed during the visit, and referral information for a trans-affirming dermatologist was provided. Test results came back positive for pharyngeal gonorrhea infection; HIV antibody testing was negative. She was treated for gonorrhea, started on PrEP, and was able to schedule an appointment the following week for initiation of feminizing hormone therapy.

Conclusion

Providers can have a significant impact on the well-being of SGMY. By adopting affirming practices at each step of the clinical encounter, healthcare staff can communicate that all young people are welcome, valued, and respected, regardless of sexual orientation or gender identity. Providers have an opportunity to connect with adolescents regarding important and complex aspects of their identity and at times may be the only adult in a young person's life with whom these issues can be discussed. Counseling youth about sexual and gender identity development and offering inclusive sexual health services, resources for gender-affirming hormones, preventative care such as vaccines and PrEP, and comprehensive family planning are all ways that providers can have a positive impact on the health of SGMY while also addressing the many health disparities that they face. By taking steps to provide supportive, inclusive care, providers have the opportunity to form meaningful relationships with SGMY and to help foster the resilience and personal agency that will set them up for a lifetime of health and wellness.

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Chapter 3
Racial Disparities in STIs Among Adolescents in the USA

Jessica M. Sales, Anna Newton-Levinson, and Andrea L. Swartzendruber

Adolescents, particularly females, young people of color, and those with lower socioeconomic status, are disproportionately affected by sexual transmitted infections (STIs) [1]. In 2015, young people 15–24 accounted for nearly two-thirds of STI diagnoses in the USA [1]. Rates of STIs are also increasing among adolescents (ages 15–19). Chlamydia, gonorrhea, and syphilis rates rose for both young women and men in this age category from 2014 to 2015 [1]. Adolescent females experience higher rates of STIs than adolescent males but also seek and receive more STD-related screening than do males [1, 2]. One in four females 14–19 years of age in the USA is infected with *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, *Trichomonas vaginalis*, herpes simplex virus type 2, and/or human papillomavirus (HPV) [3]. Black and Hispanic adolescents also experience disproportionately higher rates of STIs compared to their White counterparts [1]. For example, in 2015 the chlamydia rate among Black adolescents aged 15–19 was over five times greater than the rate among same-age White peers [1]. For Black women 15–19 years, the rate of gonorrhea was over 11 times that of their White counterparts. STI prevalence is highest in the Southern USA relative to other US regions, and Black adolescent females in the South have chlamydia and gonorrhea rates far above national and regional averages [1]. These disparities are correlated with several other social and structural determinants of health such as poverty and income inequality, insurance status, educational attainment, as well as immigration status [1, 3].

Several risk factors are associated with increased STI rates among adolescents; many are closely linked to developmental trajectories and life transitions that affect

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youth physically and behaviorally [4]. For instance, as described by Shirtcliff [5], puberty is associated with increases in gonadal sex hormones, which play a role in brain development and in adolescent risk-taking (e.g., risky sexual behavior) through several postulated mechanisms. Now well-documented, over the past 20 years, advances in developmental neuroscience indicate that the brain continues to develop into adulthood, and this impacts cognitive and emotional processes that affect risk-taking. The cognitive-control system in the brain, which regulates impulse control, is a slow maturing system and makes adolescence a time of heightened vulnerability for risk-taking behavior [6]. Giedd describes the cognitive-control system, which mainly consists of outer regions of the brain such as the lateral prefrontal and parietal cortices and portions of the anterior cingulated cortex, as involved in executive function tasks like planning, thinking ahead, impulse control, and self-regulation [6]. In addition, according to a review by Steinberg [7], puberty is associated with the remodeling of dopaminergic pathways in the socio-emotional brain system that influence reward salience and reward sensitivity, especially in social situations [7]. Historically, constructs such as impulsivity and "sensation seeking" have been linked to adolescent sexual risk-taking for decades. In his 1979 book, Zuckerman presents information on the personality trait "sensation seeking" which has been used to explain adolescent risk-taking behavior that could contribute to STI acquisition [8]. Sensation seeking has been associated with a variety of risk-taking behaviors including substance abuse and risky sexual behavior which can increase exposure to STIs among adolescents.

Other developmentally linked changes that uniquely increase STI risk are observed specifically for biologically female adolescents [9]. Many studies cite cervical ectopy as a reason for increased STI susceptibility in females, but particularly younger females [10–12]. Cervical ectopy allows greater exposure of columnar epithelium to the vaginal environment [9]. Columnar epithelium is thought to be more susceptible to sexually transmitted organisms including chlamydia and HPV than is the squamous epithelium that replaces it with the maturation process [9, 12].

In sum, developmentally linked changes in brain development that impact decision-making and reward processing might contribute to heightened risk-taking among adolescents [4–8]. Such developmentally linked risk-taking coupled with the biological vulnerability unique to the female genital tract may partially explain some of the gender disparities observed in STIs in the USA [9–12] However, these developmentally and sex-linked risk factors should generally be uniformly observed across adolescents regardless of race or ethnicity; thus they cannot easily explain the consistently observed racial and ethnic disparities in STIs documented in the USA. Several explanations have been posited in attempt to explain racial disparities in STIs in the USA. In this chapter, we will present five explanations including (1) differences in sexual risk behaviors, (2) differences in STI risk among sexual networks, (3) SES-related inequities disproportionately experienced by minorities that reduce access/care, (4) SES/racial inequities that indirectly increase STIs through a psychosocial/behavioral mechanism, and (5) SES/racial inequities that directly increase STI susceptibility through biological stress regulatory systems.

Differences in Sexual Risk Behaviors

Although differences in sexual risk behavior could possibly explain racial disparities in STI rates and disproportionately high rates among Black adolescents, evidence does *not* suggest that individual risk behaviors account for the disparity. Studies show that Black adolescents with low and moderate levels of sexual risk behavior are at high risk for STIs [3, 13, 14]. For example, a nationally representative study of data from the National Longitudinal Study of Adolescent Health to Adult Health(Add Health) found that prevalence estimates for chlamydia, trichomoniasis, and gonorrhea were 6.6, 5.8, and 21.0 times higher, respectively, among Blacks as compared to Whites aged 18–24 years [13]. However, nearly half of Black adolescents were categorized into groups exhibiting no or low substance use, no sexual experience, or zero or one sexual partners in the past year. In contrast, only approximately one-quarter of White adolescents were categorized in the same lower-risk behavior groups. Nevertheless, marked disparities in STI prevalence were observed among Black and White adolescents within these lower-risk behavior categories; STI prevalence was still 6–24 times greater among African Americans as compared to Whites with the same lower-risk behavior profiles [13]. Other studies have also found that Black adolescents with normative sexual behavior have substantial STI risk, and STI estimates are many times higher among Black youth as compared to White youth with the same behavior profiles [3, 14].

Differences in STI Risk Among Sexual Networks

Rather than differences in the prevalence of individual sexual behaviors, evidence suggests that racial disparities reflect environmental and social differences between racial groups [15, 16]. In particular, population patterns of exposure due to sexual mixing patterns may contribute to the disproportionately high rates of STI among Blacks and racial disparities in STI rates [17, 18]. Two specific patterns of sexual mixing, disassortative mixing in terms of sexual risk behavior (i.e., sex between individuals with different levels of sexual risk behavior) and assortative mixing in terms of race (i.e., sex between individuals of the same race/ethnic background), may substantially contribute to the disproportionate burden of STIs among Blacks. Laumann and Youm found that STIs were more widespread in Black relative to White populations because of greater levels of partnering among individuals with dissimilar levels of sexual risk among Blacks [17]. In their social network analysis, they found that Black peripheral individuals (who had only one sexual partner in the past year) were five times more likely to choose core individuals (who had four or more partners) than White peripheral individuals. Laumann and Youm also suggested that STIs stay within Black populations due to greater levels of assortative mixing by race among Blacks [17].

SES-Related Inequities Disproportionately Experienced by Minorities That Reduce Access/Care

Socioeconomic status (SES) is a fundamental social determinant of health and consists of social and material resources (e.g., education, income) and prestige (e.g., occupational status) [19]. SES-related risk factors such as chronic poverty and limited occupational and educational opportunities, frequent housing relocation, and unstable employment have adverse consequences for adolescents and have been found to be related to barriers in accessing STI care [20]. Poverty is higher among racial and ethnic minority groups than among Whites and has been found to be significantly associated with rates of healthcare utilization [21]. Poverty affects one's ability to pay for services and is also associated with whether one has insurance. Poverty also impacts other resources that are necessary to getting care such as access to transportation [22].

Evidence suggests that access to STI prevention methods, healthcare services, and prevention education are themselves shaped by individual, family, and community SES [23]. Family SES may shape adolescent and young adult sexual health service access [23, 24]. To illustrate, children in low SES families are less likely to have insurance coverage, which directly limits access to and use of preventive and medical care [25, 26]. Likewise, low SES neighborhoods may lack access to healthcare service and educational interventions, limitations that may, in turn, reduce communication about sexual health, discourage protective behaviors, and thereby contribute to sexual risk and STI acquisition [27, 28]. Schools located in neighborhoods with lower SES may be less likely to offer comprehensive sex education, thus narrowing awareness and knowledge of STIs. Awareness and knowledge of STIs is also associated with STI care seeking [29].

Having health insurance has also been shown to be associated with STI risk and STI testing among adolescents [2, 26, 30]. Moreover, the cost of services in general is often associated with STI care seeking for adolescents [2]. Given confidentiality concerns that also drive care seeking, adolescents may opt not to use insurance even when they have it, thus making the cost of services an even more significant barrier [2, 29]. Adolescents generally have low levels of healthcare utilization, especially for STI-related care [2]. Racial and ethnic minorities, especially Black and Hispanics, are also less likely to have access to or seek healthcare generally and often do not have a regular healthcare provider [31–33]. Blacks are more likely to get care at health departments and emergency rooms than Whites, reflecting challenges in accessing regular care such as high costs [34]. Several factors disproportionately experienced by minorities, therefore, are linked with reduced access to or willingness to seek care. These factors are social and structural as well as personal [31, 35].

Healthcare and STI-related care seeking for minority adolescents may be further limited by a general mistrust of and negative experiences with the healthcare system. Historical and current experiences of discrimination and mistreatment can lead to wariness about health services in general [31, 36]. Experiences with providers whom clients perceive to be judgmental, prejudiced, or hostile can undermine minority adolescents' willingness to seek services as well [29, 30, 36–38].

As Valentine illustrates, for adolescents "implicit and explicit messages about partners" can sound like a provider is accusing them of being sexually irresponsible or promiscuous – which may not reflect their actual or perceived behaviors [36]. Addressing these disparities and concerns requires integrating cultural competency with trust and rapport building in relation to adolescent clients in to clinical services. Such rapport building would include facilitating interactions that are non-judgmental and demonstrating a respect for patient's dignity and problem-solving abilities and their right to make their own decisions [31, 36].

SES/Racial Inequities Indirectly Increase STIs Through Psychosocial/Behavioral Mechanisms

Another potential explanatory hypothesis is that low SES, measured at the family or neighborhood level, is associated with heightened exposure to violence and other stressors, which subsequently contribute to psychosocial and behavioral risks, thereby increasing the likelihood of contracting an STI. In other words, chronic exposure to low SES, which is disproportionately experienced by Blacks and other minorities in the USA, may increase exposure to and probability of experiencing adverse life events that can contribute to trajectories of behavioral pathology (e.g., adolescent delinquency, depression). These pathologies have been associated with increased engagement in high-risk sexual behaviors [39, 40], suggesting a complex, indirect mechanism by which SES risk, which is disproportionately experienced by racial/ethnic minorities in the USA, may increase STI acquisition.

Evidence integrated from multiple studies suggests several indirect pathways between SES and STI risk depicted in Fig. 3.1, but, to date, few studies have comprehensively tested it in a single sample. Turning to the first segment of the pathway (SES→violence and other stressors), studies have linked low family SES and low neighborhood SES to heightened exposure to violence, trauma, and other stressors (e.g., racial discrimination). Childhood family income, for example, is correlated with many social and physical stressors, including family conflict, exposure to violence, and elevated parental harshness [41–44]. Poor neighborhoods have more violent crime and social and physical disorder, and families in poor neighborhoods experience more intimate partner violence and child abuse [45–47].

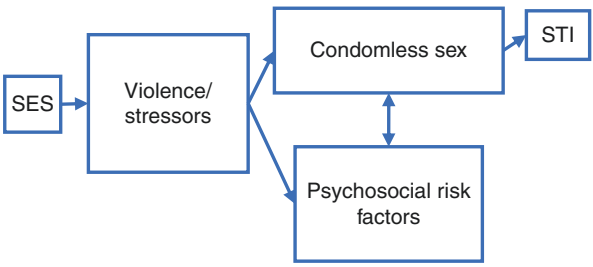

Fig. 3.1 Indirect pathways between SES and STI risk

Another body of research has focused on the second and third segments of the pathway (experiences of violence and other stressors→psychosocial risks and condom use, which in turn→STIs). Many of our own studies with adolescent African American girls and young African American women have consistently indicated that a history of abuse or exposure to other stressors (e.g., racial discrimination, interpersonal stress) is related to increased sexual risk, substance use, depressive symptoms, and STIs [48–57]. Others have corroborated these findings for families and reached parallel findings for neighborhood and school exposures to violence [58–66]. Importantly, several of our own longitudinal studies with adolescent African American girls and young women indicate that depression, sexual risk-taking, and substance use behaviors are linked to one another and/or co-occur and that each contributes to increased risk of STIs both cross-sectionally and longitudinally [39, 40, 56].

Two recent studies come close to testing this hypothesized mechanistic pathway linking SES to STIs. Wickrama et al. identified a direct association between community-level socioeconomic disadvantage during childhood and STI prevalence in a nationally representative sample of young adults [67]. Importantly, Wickrama's study also found that adolescent adjustment difficulties and risky sexual practices only partially mediated the relationship between SES-related factors, suggesting that other undetermined mechanisms may also mediate this relationship [67]. Using a prospective design, Sales et al. (2014) tested the hypothesis that SES-related risk measured at baseline assessment during adolescence predicts STI acquisition and reinfection over 36 months of follow-up while controlling for other factors associated with disparities in STI acquisition such as age, sexual risk behaviors, STI history, coping, other stressors (interpersonal stress), and mental and physical health, among a sample of African American adolescent females residing in the Southern USA [52]. SES-related risk predicted both STI acquisition and reinfection in this study. Contrary to the Wickrama study, in the Sales et al. study, sexual risk, mental health ratings, and coping were included in analyses to account for these demonstrated influential psychosocial/behavioral factors on STI acquisition, yet they were not significantly predictive of STI acquisition when SES-related risk was included in the models [52]. Thus, findings from these two exemplar studies do not completely explain the observed association between SES and STIs, but they both posit that STI disparities observed in late adolescence or early adulthood may be linked to earlier life experiences, particularly experiences associated with low SES conditions and stress exposures, which can cause significant chronic strain on an individual and thereby place them at heightened biological risk for STI.

SES/Racial Inequities That Directly Increase STI Susceptibility Through Biological Stress Regulatory Systems

Research suggests that coping with stressors, and particularly SES-related stressors, which tend to be chronic rather than acute, elicits a cascade of biological responses that are functional in the short term but over time may "weather" or damage systems that regulate the body's stress responses [68], including the sympathetic adreno-

medullary system (SAM), the hypothalamic-pituitary-adrenal (HPA) axis, lipid metabolism, fat deposition, indices of inflammation, and immune functioning [68, 69]. When coping demands are high or prolonged due to exposure to chronic stressors, the body actively mobilizes resources in response to the stressor. Some individuals become less efficient at ceasing the multifaceted physiological response resulting from chronic stress exposure, even during periods of relative calm [68, 69]. The inability to "turn off" the demand response results in physiological changes that can play a part in the development of chronic illnesses and poorer reproductive health outcomes, many of which are more prevalent among African Americans, including hypertension, cardiac disease, diabetes, and preterm and low-weight births [69–72]. Chronic stress has also been associated with suppression of both cellular and humoral immune function, resulting in heightened risk for immune-related disease and infection susceptibility and severity among adult samples [73–76].

Within the STI literature, chronic stress has been associated with HIV susceptibility and progression [74, 77] and increased incidence of bacterial vaginosis (BV) even when accounting for common risk factors such as frequency of sexual intercourse, douching, and lifetime sexual partners [76, 78]. Interestingly, BV has a higher incidence among Black women compared to Whites [79, 80], and its occurrence can place women at increased risk for acquisition of subsequent STIs, such as chlamydia, gonorrhea, and trichomoniasis [24].

Despite the role that SES-related stress or other chronic stress exposures may play in the development of chronic diseases and health disparities disproportionately observed in Black individuals [70], virtually no studies have focused on this as a potential pathway by which Black adolescents may be at increased risk of STI acquisition. Outside of STI outcomes, several studies have found that individuals from low SES families are more frequently diagnosed with respiratory, urinary, and reproductive tract infections [80, 82], providing support for the hypothesis that low SES may negatively affect immunity. Experimental studies suggest a causal relationship: when challenged with respiratory viruses, individuals with low SES are more likely to demonstrate symptoms and signs of clinical infection than individuals with higher SES [83–86]. While various behavioral, environmental, and nutritional factors may explain these socioeconomic disparities in disease susceptibility, immune dysfunction resulting from economic hardship-induced stress may also play a role. In sum, given the potential for increased STI susceptibility due to reduced immune function and the reported increase in risk for predisposing infections such as BV [74, 76–81], the role of chronic stress, such as that resulting from exposure to high SES-related risk during childhood and adolescence on prospective STI infection, is warranted and has yet to be empirically examined.

Conclusion

In sum, adolescents disproportionately experience STIs at higher rates than adults in the USA, but the STI burden is not equally distributed among the adolescent population. Racial minority youth, particularly Black adolescents in the USA, expe-

rience STIs at much greater rates than their age-matched White counterparts. Many hypotheses have been put forth to explain the racial disparity in STIs in the past 30 years, with some having weak evidence (e.g., difference in sexual risk behaviors, which is clearly not a factor contributing to Black-White STI disparities) and others having more substantial but still insufficient evidence (e.g., disparities operating through psychosocial/behavioral mechanism). It is likely that none of these single hypotheses alone can fully capture the complex contextual and structural forces that often drive health disparities among minority populations in the USA, and they should be examined in combination to advance our understanding of which elements have more explanatory merit. Regardless, healthcare providers providing sexual health services, including STI services, to minority youth should be aware that it is primarily external contextual and structural factors, rather than heightened sexual risk-taking, that contribute to STIs among this population when treating youth. Additionally, healthcare providers working with adolescents should be aware of adolescent and minority adolescent wariness of healthcare providers and reported experiences of stigma in the context of sexual healthcare when providing care for youth. To ensure adolescent patients feel safe and supported during sexual health visits, providers should engage with adolescents in non-stigmatizing manner that does not place individual blame or judgment related to their behavior when conducting STI testing and treatment particularly.

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Chapter 4
Ethical and Legal Considerations in STI Treatment for Adolescents

Quianta L. Moore

Case Study
A 15-year-old girl comes to her pediatrician's office for an acute care visit. Her chief complaint is pain with urination that started a week ago. She also complains of a greenish-yellowish vaginal discharge. While taking her history, she reveals that she is sexually active with both male and female partners and only occasionally uses condoms. Her last sexual encounter was with a man who she met on a social networking app. She has never been tested for HIV or any other sexually transmitted infections (STI). She came to the visit alone, paid with cash, and does not want her parents to know about her visit to the clinic. Her pediatrician wants to conduct HIV and STI testing, as well as a well-woman exam, but is unsure of whether he can legally do so without parental consent or whether he can promise that her parents will not find out about the visit.

Questions
- Can minors consent to diagnosis and/or treatment for HIV and other STIs without parental permission?
- If parental consent is *not* required for HIV and STI diagnosis and/or treatment, are there any other legal or ethical obligations that would require disclosure to parents of diagnosis and/or treatment?

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The concept of informed consent is rooted in principles of respect for autonomy and protection of individuals' property and bodies [1] from unauthorized invasion. Informed consent has influences that originate in tort law [2], in international declarations [3], and in basic bioethical principles [4]. An individual's informed consent must be knowledgeable and voluntary, and it conveys a decision in favor of a proposed course and the authorization to proceed [5]. Obtaining informed consent from patients prior to treatment is a legal requirement. However, patients must have decision-making capacity in order to provide consent. Adults are generally assumed to have decision-making capacity unless there is evidence that their cognitive function has been impaired. In contrast, individuals under the age of majority (age 18 in most states) are by default assumed to not have decision-making capacity, and therefore consent must be obtained by their legal guardian (hereafter we will refer to both parents and other legal guardians using the term "parent"). Parents legally have the right to make decisions for their children, as the law's concept of family rests on the presumption that parents possess what a child lacks in maturity, experience, and capacity for judgment [6]. Additionally, the law assumes that parents will act in the best interest of their children [6]. However, there are situations where the law recognizes that children, particularly adolescents, should have the right to provide informed consent for themselves.

The determination of one's right to consent is typically determined by state law. The circumstances in which adolescents can consent to their own medical care vary by state and are generally divided into two categories: (1) minor is legally treated as an adult or (2) medical care for certain conditions or diseases permits minor consent.

Minor Status

Whether an adolescent patient can provide consent to medical care and services depends upon his or her status as a minor or adult. Except in Alabama [7] and Nebraska [8] where the age of majority is 19, an individual is a minor if he or she is under the age of 18 (age of majority). In Mississippi, minors are considered adults for the purpose of consenting to medical care, but otherwise the age of majority is 21 [9]. Even when an adolescent is under the age of majority, there are exceptions in which the minor may still legally be considered an adult.

Emancipation

Minors can obtain legal status as an adult by a court of law. Most states have specific statutes or court cases that specify the circumstances under which a minor can be emancipated from his or her parents prior to reaching the age of majority. The most common circumstances are military service, marriage, or independently managing one's own finances and living separate from his or her parents. Emancipated minors can consent to medical services for themselves as well as enter into contractual agreements. Although law may not require proof of emancipation, it is prudent for

physicians to have documentation of status prior to performing medical services because performing medical services, without lawful consent, could be considered battery in a lawsuit.

Mature Minors

The mature minor doctrine arose out of common law, which is law that is derived from court cases. As such, application of the common law largely depends on the consistency of the facts of the present situation with the facts of the court case. For instance, Maine's mature minor common law doctrine is limited to admissibility of statements a minor made about being in a persistent vegetative state [10]. However, some states have codified the common law doctrine into statutes, which provide physicians with more certainty and clarity on how to apply the law. In either legal environment, physicians must have a clear understanding of how or if this doctrine is applied in their state and whether the doctrine is common law or statutory law. Currently, there are only 14 states that recognize a mature minor exception to the general requirement of parental consent [11].

In general, the doctrine allows individuals under the age of majority to consent to non-emergency care, especially when the risk of treatment is considered low. In the states that recognize the mature minor doctrine, application of the doctrine relies heavily on the clinician's assessment of the individual's ability to understand the risks and benefits of the proposed medical care and ability to provide the same level of informed consent as an adult. Determining the minor's ability to provide the same level of consent requires that the physician assess whether the primary components of decision-making capacity are present. The primary components of determining decision-making capacity are (1) paying attention to the information provided, (2) recalling information when needed, (3) reasoning from present events to future likely consequences, (4) appreciating that those consequences could happen to them, (5) assessing those consequences on the basis of their values and beliefs, and (6) expressing a preference on the basis of the previous components [12]. Additionally, the individual should be at least 14 years old, which is consistent with the age when adolescents should, from a developmental perspective, have the cognitive and decision-making capacities similar to those of adults [13, 14].

Even if treating a minor is legally permissible under the mature minor doctrine, physicians should consult the policies of their particular practice and document the decision-making capacity evaluation of the minor as well as any other facts that justify the physician not obtaining parental consent for the general medical care of the minor.

Exceptions for Sexually Transmitted Infections

In contrast to the state-to-state variability in applying the mature minor doctrine, every state has created a statutory exception to parental consent for medical care related to sexually transmitted infections (STIs). All 50 states and the District of

Columbia either have a statute expressly authorizing minors to consent to the diagnosis and/or treatment of a STI or implicitly authorizing minor consent by stating minors may receive the services without parental consent [11]. In a very small number of states, a separate statute is not created for minor consent to STI, but rather an exception is outlined in the general consent statute [11]. Of note, many of the statutes use outdated terminology (such as *venereal disease*) or include STIs in a broader definition of communicable diseases [11]. Regardless, physicians can be confident that a minor seeking medical care for a STI has a legal right to consent to either the diagnosis or treatment of the STI without parental consent. Thus, a physician may legally conduct necessary testing on a minor to obtain a diagnosis of STI in all states, but physicians must be aware of whether their particular state permits *treatment* without parental consent.

Confidentiality

The confidentiality of minors is regulated at both the federal level through the Health Insurance Portability and Accountability Act (HIPAA) and at the state level through various state consent and confidentiality statutes. HIPAA generally gives parents the right to access their child's health information unless (1) the parent waived his or her right to access, (2) the medical care was court ordered, or (3) the minor consented to the medical care under state law (and parental consent was not required) [15]. Thus, whether a parent has the right under HIPAA to access a minor's private health information depends on the minor consent laws within that state. Since all 50 states permit minors to consent to STI diagnosis, physicians would not be required under HIPAA to disclose STI testing to the minor's parents. Some states have explicit statutes that protect minor's confidentiality for STI medical services [11]. On the other hand, some state statutes require disclosure to parents or other entities if the results are positive. For instance, South Carolina's law requires reporting of STIs to a state agency and notification of a positive HIV test to the minor's superintendent and school [16]. Disclosure of patient health information to schools can make health information that was otherwise confidential accessible to parents through the Family Educational Rights and Privacy Act. This law gives parents the right to access the education records of their minor children [17]. If health information is contained within those records, that information would be accessible by parents, even if they were unable to obtain those same results directly from healthcare providers.

Some states treat HIV differently than other STIs. For instance, Iowa prohibits the disclosure of a STI unless the minor tests positive for HIV, in which case the physician must notify the minor's legal guardian [18]. Overall, physicians should be aware of the state laws in which they practice because even when HIPAA does not require disclosure, state law may create additional rights and obligations for physicians to report or disclose.

If state or other applicable law is silent on a parent's right to access their minor child's health information, the physician may exercise his or her professional judgment, as allowed by law, to grant or deny parental access to the minor's STI-related medical information. For instance, Idaho is silent on STI confidentiality protections, in which case physicians can use their discretion [19]. Louisiana permits physicians to disclose STI-related medical care to parents over any objection of the minor [20]. Statutes that explicitly permit physicians to use their discretion provide more legal protection in the event the physician's decision is questioned in court. There are 18 states that allow (but do not require) physicians to disclose a minor's STI information to their parents [21].

Even if legally permissible under state law, physicians should weigh the ethical and public health considerations of maintaining minors' confidentiality prior to disclosure. States likely created statutory provisions for minors to access STI services without parental consent because of public health and safety concerns that minors would not seek treatment if parental consent was required. Early diagnosis and treatment are paramount to stopping the spread of STIs. Likewise, research demonstrates that parental disclosure of the receipt of STI medical services may deter minors from seeking treatment [22]. For instance, a randomized controlled trial of 562 adolescents demonstrated that adolescents were more willing to disclose sensitive information about sexuality, mental health, and substance abuse when the physician provided absolute confidentiality [23]. Confidentiality protections also increased the number of adolescents willing to seek future healthcare [23]. In contrast, 59% of adolescents ($n = 950$) reported in a survey administered to minor girls in Wisconsin that they would discontinue sexual health services, including testing and treatment for HIV and other STIs, because of parental notification [24]. The ways in which parental disclosure may affect a clinic's adolescent patient population, and by extension the public health of the community being served, should be carefully considered. Public health and ethical justifications should be considered, along with the benefits and harm to the patient, in any decisions about minor confidentiality.

Physicians may want to consider the ethical implication of their decision to disclose to parents on a case-by-case basis. Factors that should be considered are (1) maturity level of the adolescent, (2) minor's relationship with parents, (3) harm caused if minor's confidentiality is breached, (4) urgency or seriousness of condition, (5) respect for parents, (6) harm of not disclosing to parents, and (7) fiduciary duty to the patient [25]. These factors will aid in guiding a thoughtful analysis of the risk and benefits of parental disclosure.

If a well-thought-out analysis for every adolescent patient is burdensome, it would benefit physicians to have a policy in place that explains their practice's parental disclosure policy. Such policies should be developed in consultation with an attorney to ensure adherence to applicable state and federal laws. If a physician works within a large physician group and/or hospital system that treats adolescents, those organizations likely have minor consent and confidentiality polices in place. Additionally, physicians should consult the position statements of their professional

organization. The American Academy of Pediatrics (AAP) encourages minors to talk with their parents about the medical services received and emphasizes the importance of respecting their parents' role in acting in the best interest of their children [26]. Likewise, some states have statutory language encouraging physicians to persuade minors to disclose medical information to their parents, which would avoid breaching the minor's confidentiality [27]. However, if the physician determines that parental notification would hinder the care of the patient, ultimately the AAP supports an independent patient-physician relationship with the minor patient and confidentiality protections reflective of an independent patient-physician relationship [26]. Ultimately, physicians should have a clear framework in mind for handling parental notification and disclosure of STI services performed on minors. State and federal law, public health and ethical considerations, and institutional and professional guidelines should inform the development of any framework and/or policy regarding parental disclosure of minor's sexual health services.

Case Conclusion

In all 50 states, minors can receive STI testing, including HIV testing, without parental consent. Therefore, her physician can perform STI testing. However, unless the physician is practicing in a state that allows the mature minor doctrine, or the minor is emancipated, the physician cannot perform general medical care of the minor, which includes the well-woman exam. The majority of states also permit STI treatment without parental consent. Therefore, it is likely the minor can be treated for a STI if the results are positive. However, it is not recommended for physicians to interpret the law on their own. Consultation with an attorney regarding state law and institutional policy is absolutely necessary prior to initiating treatment. Many states treat HIV differently, and therefore it is possible that HIV treatment could not be initiated without parental consent or notification, and it should be emphasized that consultation with legal counsel will help to determine what is and what is not permitted without parental consent in the state in which the physician practices.

Even if state law permits the patient to consent to both diagnosis and treatment, disclosure to parents of the medical services received will likely be up to her physician. There are a few states that prohibit disclosure, but most state statutes are deferential to physician's discretion. Hopefully, the physician has a policy in place that can be referred to when making the decision of whether to maintain the minor's confidentiality, regardless of the test results.

There are also financial considerations of treating minors without parental consent and/or notification. This patient paid with cash so that her parent's insurance would not be notified of the visit. However, many adolescent patients may not have the resources to pay cash for their medical care. When adolescents use their parent's insurance, insurance companies in the majority states (a few states prohibit this) [11] will notify the parents. Moreover, when minors can legally consent to a medical service, many states have laws that protect the parents from financial responsi-

bility [28]. When the minors have limited resources, and the parents are not obligated to pay for their medical care, physicians can be left with uncompensated care. Physicians should be aware of the financial responsibility laws in their state and have policies in place to help avoid nonpayment. For instance, this case suggests the physician already had a relationship with the minor. General medical care of the minor would have required parental consent, at which time the physicians could have established an agreement that any care provided to the minor, even without the parents' consent, would be paid for by the parents.

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Part II
Common Clinical Syndromes

Chapter 5
Vaginitis and Cervicitis

Anar S. Patel and Anandi N. Sheth

Case Study

Anna is a 19-year-old female college student who presents with thin, white vaginal discharge with foul odor which started 1 week ago. She also endorses mild itching in her genital region which is quite bothersome. She is otherwise healthy and takes combined oral contraceptive pills and a multivitamin daily. She is sexually active with two male partners and occasionally uses condoms. Anna smokes approximately one fourth of a pack of cigarettes per day. She reports that she tried drinking cranberry juice for her symptoms without any improvement. Examination reveals non-edematous vaginal walls coated with thin, gray secretions with a "fishy" odor. Wet mount in the clinic demonstrates vaginal epithelial cells covered with bacteria. The pH of vaginal secretions is measured at 5.3. A pregnancy test is negative, and a cervical swab specimen is sent for gonorrhea and chlamydia PCR.

Case Questions

1. What clinical syndrome does the patient exhibit?
2. What diagnostic tests would be helpful in identifying the etiology of the patient's symptoms?
3. What counseling should be given to the patient to reduce her risk of this disease recurring?

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Introduction

Symptomatic vaginal discharge is a common reason for women to seek medical care [1]. Vaginal discharge may be normal or pathologic, and self-diagnosis and self-treatment frequently occur [2]. Vaginitis is usually characterized by vaginal discharge, vulvar itching, burning, irritation, and odor and may have either infectious or non-infectious etiologies [3]. Common infectious etiologies include bacterial vaginosis (BV), vaginal candidiasis, and trichomoniasis. Non-infectious etiologies of vaginitis include dermatologic etiologies of vaginitis, such as allergic vaginitis and vulvar vestibulitis. The presence of purulent vaginal discharge raises concern for cervicitis, which also can be infectious or non-infectious in etiology [2]. Infectious mucopurulent cervicitis can be caused by *Chlamydia trachomatis*, *Neisseria gonorrhoeae*, herpes simplex (particularly primary HSV-2 infection), *Mycoplasma genitalium*, *Trichomonas vaginalis*, and *Candida albicans* [4].

Normal and Abnormal Physical Exam

Treatment of vaginal complaints based solely on patient symptomatology alone has not been shown to accurately correlate with final diagnosis [1]. Therefore, detailed history taking, physical exam (including speculum pelvic examination) and other diagnostic tests are essential in determining the causes of vaginitis [5, 6]. Medical history of the patient should include their age, other medical conditions and medications (including those that may cause immune suppression), menstrual history, prior pregnancies and current pregnancy status, sexual preference and practices, use of intravaginal products, past and current sexual relationships, condom use, and prior genitourinary infections. Regarding the patient's symptom history, key features to elucidate include timing of symptom onset, quality and quantity of discharge, presence of irritation or burning, odor of vaginal discharge, and presence of abdominal pain or discomfort and any constitutional symptoms.

Vaginal discharge may be physiologic or pathologic, and differentiation between the two can often be ascertained based on history alone. Vaginal secretions are a physiologically important aspect of a healthy female genitourinary tract. Glycogen-containing vaginal cells depolymerize after they are shed into the lumen of the vagina and serve as an energy source for a group of bacteria that live in the healthy vagina known as lactobacilli [2]. The vaginal microbiome, or the community of bacteria that live in the vagina, is dominated by species of *Lactobacillus* which has long been thought to be protective in the vaginal ecosystem. *Lactobacillus* species produce lactic acid that keeps the vaginal pH to a protective level of less than 4.5. They also serve as a barrier to infection through the production of bacteriocins which prevent the overgrowth of unhealthy vaginal bacteria. Normal vaginal discharge is a combination of vaginal epithelial cells and *Lactobacillus* species bacteria in fluid that appears clear to white in color and is highly viscous and odorless [2, 3]. The volume of vaginal secretions may vary between women and is often influenced by the phase of the menstrual cycle, pregnancy, and the use of hormonal contraceptives [2]. Cervical mucous also increases in the pre-ovulatory phase of the menstrual cycle and peaks at mid-cycle [2, 7, 8].

A general physical examination should be performed for all patients undergoing evaluation for vaginitis. Suprapubic and abdominal examination should be undertaken to assess for tenderness, masses, and inguinal adenopathy [2]. Gynecologic examination requires careful inspection of the external and internal genitalia for lesions or ulcerations. The appearance and integrity of vulvar and perineal skin may reveal clues to the underlying diagnosis. Speculum examination involves inspection of the vagina and cervix for lesions or ulcerations as well as collection of samples of vaginal secretions for vaginal wet mount examination and other laboratory testing [2]. Vaginal and cervical mucosal inspection should include attention to erythema, friability, and lesions in addition to notation of an ectropion, if present [2] (Fig. 5.1). Cervical ectropion occurs when the endocervix exposes columnar epithelium to the vaginal environment due to eversion; ectropion is a normal finding and common in adolescents, pregnant women, and those taking estrogen-containing contraceptives [9]. Bimanual examination is necessary for evaluation of cervical motion tenderness, adnexal tenderness, and uterine or adnexal masses [2].

A vaginal wet mount can be prepared by mixing the vaginal fluid with 0.5 mL of normal saline to form a suspension. This fluid suspension undergoes the "whiff test" for odor before being placed on a microscopic slide to form a wet mount [2]. If available, a pH meter or colometric strips can be utilized to determine the pH of the sample or can be tested directly on vaginal wall. The wet mount should be examined under high-power microscopy for both number of epithelial cells and presence of polymorphonuclear neutrophils (PMNs). Increased number of PMNs can be suggestive of vaginal or cervical inflammation. Importantly, identification of parasitic, bacterial, and fungal organisms can aid in the diagnosis of vaginitis [2] (Fig. 5.2). Application of a drop of 10% potassium hydroxide (KOH) on the slide can enhance a "fishy" odor if present and highlight the presence of yeast with pseudohyphae [10]. While the vaginal fluid wet mount is an essential test due to its point-of-care availability, it has low sensitivity for diagnosis of many vaginal infections [10], and laboratory-based diagnostic testing can additionally support the clinical diagnosis of vaginitis and cervicitis and identify the causative pathogen [11]. Gram stain, culture, nucleic acid techniques, and PCR testing provide alternative methods of testing, though in some settings, the costs and availability of these methods may preclude clinical utility [10]. Nuclei acid amplification tests (NAAT) of vaginal fluid may be particularly useful for diagnosing sexually transmitted infections (STIs) such as *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, and *Trichomonas vaginalis* [2].

Bacterial Vaginosis

Epidemiology

Bacterial vaginosis (BV) is the most common cause of vaginitis [3], affecting up to 30% of women in the United States [12]. Bacterial vaginosis occurs in reproductive age women worldwide [13], and its prevalence can vary within a population [3]. While it is not considered a sexually transmitted disease, there are higher rates of BV

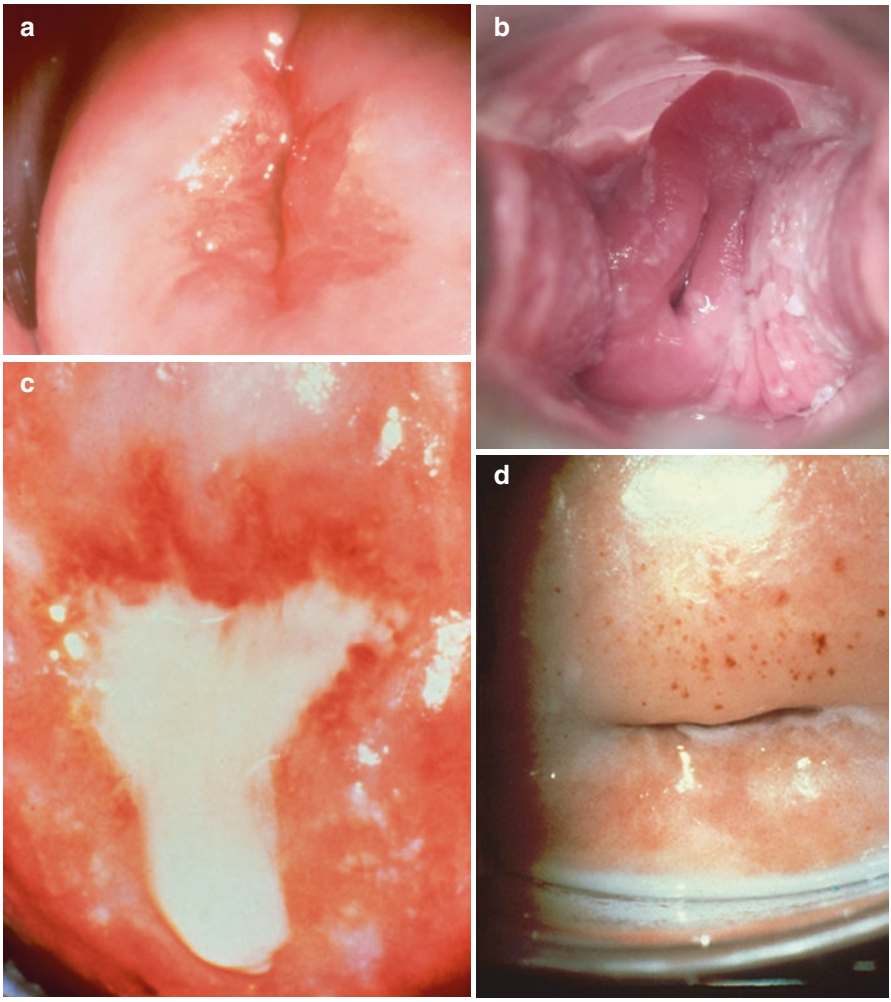

Fig. 5.1 Common findings on cervical and vaginal inspection. Images **a**, **c**, and **d** provided by the University of Washington STD Prevention Training Center with permission. (**a**) Cervical ectropion in an adolescent women; (**b**) adherent, thick, white "cottage cheese" discharge consistent with vulvovaginal candidiasis; (**c**) cervical friability with mucopurulent discharge consistent with cervicitis; (**d**) cervical petechiae or "strawberry cervix" consistent with trichomoniasis

in women with multiple sexual partners [11]. In particular, there is a strong association between BV and having female sexual partners [14]. Other risk factors for BV include black race, chronic stress, poverty, dietary factors, douching, cigarette smoking, menses, and the presence of an intrauterine device [12]. Studies have also shown that the dysbiosis associated with BV also increases risk of acquiring STIs, such as gonorrhea, chlamydia, genital herpes, and human immunodeficiency virus (HIV) [15, 13]. BV is linked to serious sequelae in the upper genital tract, particularly in the

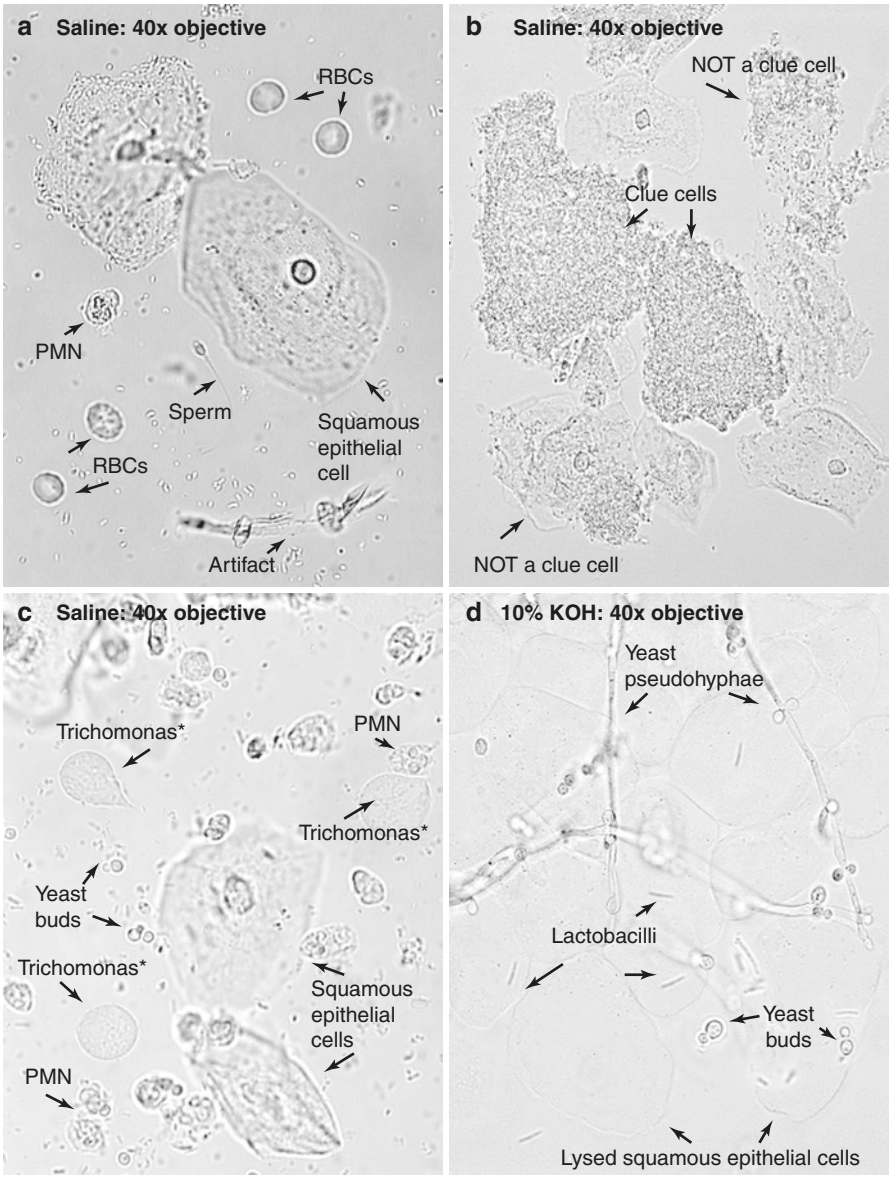

Fig. 5.2 Summary of vaginal fluid wet mount findings (40× magnification). Images **a**–**d** provided by the University of Washington STD Prevention Training Center with permission. (**a**) Normal wet prep with vaginal epithelial cells; (**b**) wet prep demonstrating clue cells and leukorrhea; (**c**) wet prep with trichomonads; (**d**) wet prep with pseudohyphae after 10% potassium hydroxide

setting of pregnancy, including premature rupture of membranes, premature delivery and low birthweight, postoperative infections after hysterectomy, development of pelvic inflammatory disease [3], and spontaneous abortion [13].

Pathophysiology

BV represents a condition in which the normal protective lactobacilli [11] are replaced by an increased number of facultative anaerobes [13] and cause symptomatic vaginitis. The vaginal pH is normally maintained at a healthy level of less than 4.7 by protective lactobacillus species, particularly *L. crispatus* and *L. jensenii* [11]. Lactobacilli hydrolyze glycogen and produce hydrogen peroxide [3] which helps maintain a low pH that is associated with healthy pregnancy and decreased risk of sexually transmitted infections [11]. In BV, this healthy microbiota shifts to one that is dominated by anaerobic coccobacilli and gram-negative bacteria, including *Gardnerella vaginalis*, *Prevotella*, *Megasphaera*, and *Mobiluncus* species [2]. A shift in vaginal microbiota causes symptoms in 60% of patients, though it is not known why some patients develop symptoms and others do not [11].

Diagnosis

Patients with symptomatic BV complain of gray, milky vaginal discharge, often with a "fishy" odor. The fishy odor is caused by the metabolism of anaerobic bacteria resulting in volatized amines at an increased pH [2, 11]. These symptoms may be more prominent after sexual intercourse or during menses when the pH of vaginal secretions increases [3]. Microscopy reveals the presence of "clue cells," which are vaginal epithelial cells with a heavy coating of bacteria [10] (Fig. 5.2). Amsel's criteria is widely used to diagnose BV and includes meeting three of the four of the following clinical criteria: (1) thin, homogenous vaginal discharge, (2) vaginal pH > 4.5, (3) positive whiff test ("fishy" odor when KOH is added to vaginal fluid), and (4) the presence of significant (>20%) amount of clue cells on wet mount [5, 16]. The efficacy of clinical diagnosis and microscopy are dependent on clinician experience [17]. The preferred laboratory method for diagnosis of BV is gram stain of vaginal fluid with a standardized scoring method known as the Nugent's score. The vaginal smear is fixed with routine gram stain procedure and analyzed under oil immersion for types of bacteria: large gram-positive rods (*Lactobacillus* morphology), gram-negative rods, small gram-variable rods (*Gardnerella vaginalis*), and curved gram-variable rods (similar to *Bacteroides* species) [10]. A score between 0 and 4 is given for each based on the presence and quantity of each morphotype, and a total score of 7–10 is consistent with BV [17]. Polymerase chain reaction (PCR) assays and culture methods have been studied for the diagnosis of BV but are not widely validated for use [11].

Treatment

The mainstay of treatment for BV in nonpregnant women is oral metronidazole 500 mg twice daily for 7 days [3] (Table 5.1). The recommended topical treatment regimens which have been shown to have equivalent efficacy though possible increased rate of recurrences [1] include metronidazole gel 0.75% one full applicator (5 gm) intravaginally once or twice daily for 5 days or clindamycin gel 2% applicator (5 gm) intravaginally once daily for 7 days. Tinidazole 2 gm daily for 2 days, tinidazole 1 gm daily for 5 days, and clindamycin 300 mg twice daily for 7 days are approved oral alternatives [3]. The FDA has approved metronidazole 750 mg extended-release tablets once daily for 7 days and a single dose of clindamycin vaginal cream [2]. Short-term cure rates following first-line therapy approach 80%; however extended follow-up shows that recurrence rates exceed 50% in the first 6–12 months. High recurrence rates have led investigators to alternative therapeutic approaches including extended and suppressive antimicrobial regimens, non-pharmacological methods, and adjunctive therapies [13]. Twice weekly intravaginal metronidazole gel for 4–6 months has been suggested to reduce recurrences [3]. Limited data exists for the use of tinidazole followed by intravaginal boric acid 600 mg at bedtime for 21 days and then suppressive 0.75% metronidazole gel twice weekly for 4–6 weeks in cases of recurrent BV [2, 18] (Table 5.1). Alcohol consumption should be avoided during treatment with nitroimidazoles, and abstinence should continue up to 72 hours after the last dose of tinidazole to prevent a disulfiram-like reaction [18]. Topical clindamycin preparations are oil-based and might weaken latex condoms and contraceptive diaphragms for up to 5 days after use [18]. Treatment of male or female sexual partners is not recommended for women diagnosed with BV. Risk reduction methods should be discussed with all women diagnosed with BV including correct and consistent condom use and limiting number of sex partners and avoidance of douching to reduce the risk of relapse [3].

Pregnancy Considerations

Pregnant women with BV can suffer adverse pregnancy outcomes including premature rupture of membranes, early labor, preterm birth, and postpartum endometritis. Symptomatic BV in pregnancy should always be treated [2]. While studies show reduced rates of preterm delivery in pregnant women treated for BV who previously delivered a premature infant [19–21], the US Preventive Services Task Force (USPSTF) concluded that there was insufficient evidence to screen asymptomatic pregnant women at high risk for preterm delivery and also recommends against routine screening for BV in asymptomatic pregnant women at low risk for preterm delivery [22]. Pregnant women who are treated for BV should be prescribed one of the following regimens: oral metronidazole 500 mg twice a day for 7 days, oral metronidazole 250 mg three times a day for 7 days, or clindamycin 300 mg twice a day for 7 days; tinidazole should be avoided in pregnancy due to limited data [3].

Table 5.1 Treatment regimens for vaginitis and cervicitis by pathogen

Diagnosis	Primary treatment regimen	Alternative treatment regimens
Vaginitis		
Bacterial vaginosis	Oral metronidazole 500 mg twice daily for 7 days	Intravaginal metronidazole gel 0.75% one full applicator (5 gm) once or twice daily for 5 days Intravaginal clindamycin gel 2% applicator (5 gm) once daily for 7 days Oral tinidazole 2 gm daily for 2 days Oral tinidazole 1 gm daily for 5 days Oral clindamycin 300 mg twice daily for 7 days
Vulvovaginal candidiasis	*Uncomplicated*: Oral fluconazole 150 mg once Clotrimazole intravaginal 1% cream 5 gm daily for 7–14 days Miconazole intravaginal 1% vaginal cream 5 gm daily for 7 days Miconazole 100 mg vaginal suppository daily for 7 days	*Complicated*: Oral fluconazole 150 mg once and repeat after 3 days Clotrimazole 100 mg vaginal tablet once daily for 7–14 days
Trichomonas vaginalis	Oral metronidazole 2 gm once Oral tinidazole 2 gm once	Oral metronidazole 500 mg twice daily for 7 days (preferred treatment for HIV-infected women)
Cervicitis		
Neisseria gonorrhoeae	Intramuscular ceftriaxone 250 mg once *plus* oral azithromycin 1 gm once	Oral cefixime 400 mg once *plus* oral azithromycin 1 gm once. Concern for declining efficacy of cefixime; use only if ceftriaxone is not available
Chlamydia trachomatis	Oral azithromycin 1 gm once Oral doxycycline 100 mg twice daily for 7 days	Oral erythromycin 500 mg four times daily for 7 days
Mycoplasma genitalium	Oral azithromycin 1 gm once Oral moxifloxacin 400 mg daily for 7–14 days if previous treatment failed	–

Topical agents do not appear to be as effective as oral agents during pregnancy, and use of clindamycin cream has been associated with increased risk of infection and premature delivery [2].

Vulvovaginal Candidiasis

Epidemiology

Vulvovaginal candidiasis (VVC) is symptomatic vaginitis caused by *Candida* yeast species [23] and is the second most common cause of vaginitis in women [24]. *Candida* species can be a normal part of vaginal flora, and up to 30% of women may

be colonized [2]. In women with symptomatic VVC, *Candida albicans* is in 80–90%, and other types of *Candida* species (including *C. tropicalis* and *C. glabrata*) are isolated in the remainder [2]. The incidence of vaginitis caused by fungi other than *C. albicans* has recently been increasing and is associated with recurrent VVC and in the setting of HIV infection [2].

Pathophysiology

Normal microbiota in the vagina inhibit yeast proliferation and germination through the production of bacteriocins. Some strains of *Lactobacillus* prevent colonization of yeast in vaginal cells by producing a protein that allows attachment of lactobacillus bacteria to mucosal cells instead of yeast and thereby reduce the risk of infection caused by yeast [25]. Symptomatic VVC is caused by overgrowth of yeast in the vagina [3]. Growth of yeast and adherence to vaginal epithelial cells are promoted by high estrogen levels [2, 25]; accordingly, women who are pregnant or taking oral contraceptives have higher rates of both yeast colonization [2] and VVC [25]. Broad-spectrum antibiotics also increase the risk of VVC by eradicating normal vaginal microbiota [2, 25]. Other major contributors to VVC include diabetes mellitus, obesity, and immunocompromised medications or conditions, including use of systemic steroids or HIV infection [25]. Sexual activity and multiple sexual partners are not associated with higher incidence of VVC [2].

Diagnosis

History taking serves as a useful tool in the diagnosis of VVC, particularly if the patient provides pertinent risk factors such as exposure to antibiotics, steroids, or oral contraceptives. The patient's medical history including known diabetes and HIV status is also helpful in supporting the diagnosis [2, 25]. The most common complaint in VVC is vulvar pruritus with little to no discharge. External dysuria and dyspareunia is occasionally noted [3]. Patient may complain of thick, adherent white discharge likened to "cottage cheese" [3] (Fig. 5.2). Pale or erythematous labia with shallow, linear ulcerations on the posterior portion of the introitus are most commonly seen on physical exam. Small erythematous papules or papulopustules beyond the primary area of erythema (satellite lesions) may be present [2]. Diagnosis can be confirmed with examination of vaginal secretions mixed with 10% KOH or saline under the microscope [2] (Fig. 5.2). Microscopic examination is not sensitive but can reveal budding yeasts or pseudohyphae. Vaginal pH is typically normal [3]. Cultures are not recommended for routine diagnosis [2] but can be helpful for recurrent disease or if the wet prep is nondiagnostic in the setting of compatible history and physical examination [25].

Treatment

Treatment of VVC depends on whether infection is uncomplicated or complicated [2]. Uncomplicated VVC involves young women who are not immunocompromised with sporadic or infrequent VVC episodes with mild to moderate symptom severity [3]. These patients usually have infection caused by *C. albicans* and will respond to treatment with short courses of topical or oral antifungal agents [2]. Topical intravaginal antifungal agents for 1–7 days and oral fluconazole 150 mg in one dose are equally effective treatment options for uncomplicated VVC [3, 23]. There are minimal side effects or toxicities associated with fluconazole at this dosage, and it may be less expensive than topical agents [2].

Complicated VVC occurs in patients with underlying immunocompromised conditions including HIV, malignancy, iatrogenic immunosuppression, or diabetes mellitus. Patients who have recurrent VVC (>4 episodes per year), severe symptomatology, or non-albicans candidiasis are also considered to have complicated disease [2, 3]. Vaginal culture should be obtained in complicated VVC to confirm the diagnosis and determine the yeast species. Severe VVC should be treated with 7–14 days of topical antifungal therapy or oral fluconazole 150 mg once followed by another dose in 72 hours [3]. Recurrent VVC can be treated with 7–14 days of topical therapy or oral fluconazole in doses between 100 and 200 mg repeated every 3 days for 1 week (days 1, 4, and 7) [3]. Recurrent VVC often requires chronic suppressive treatment with an oral antifungal agent which is continued for at least 6 months, though relapse can occur after discontinuation [2]. Species other than *C. albicans* are more likely to be resistant to fluconazole; therefore, non-fluconazole therapies should be used based on fungal susceptibility testing, if available. Boric acid powder in a 600-mg dose used intravaginally once daily for 14 days has been used with success for recurrent VVC or nonresponders to conventional treatment [2, 3] (Table 5.1).

Pregnancy Considerations

Azole antifungal agents are contraindicated during pregnancy. Pregnant women with VVC should be treated with topical agents for a minimum of 7 days [2].

Trichomoniasis

Trichomoniasis is caused by the protozoan *Trichomonas vaginalis*, a sexually transmitted pathogen [2], and has been associated with vaginitis, cervicitis, pelvic inflammatory disease, and urethritis [26]. The distribution of *Trichomonas* is equal among all age groups, unlike other STIs which are more prevalent among youth and

adolescents [27]. Presenting complaints include vaginal discharge, dysuria, pruritus, irritation, and odor [27]. Examination is notable for vulvar and vestibular edema and erythema and purulent vaginal discharge [2]. Mucosal capillary dilatation of the cervix [2] visible on speculum exam is described as "strawberry cervix" [27]. While vaginal wet preparation is only 60–70% sensitive in symptomatic patients, it is quick and inexpensive to perform [27] (Table 5.2). Motile flagellated trichomonads and many PMNs can be visualized on wet mount [2]. Culture is the gold standard for diagnosis and is more sensitive than direct visualization [26]. Various culture media are commercially available including Diamond's medium and InPouch TV [2]. PCR-based tests, including the Aptima assay for *T. vaginalis* [18], have sensitivities approaching that of culture [27] and are highly specific for infection [18].

The first-line treatment for trichomoniasis is a single 2-gram dose of the oral nitroimidazoles metronidazole and tinidazole. Alternatively, a 7-day course of oral

Table 5.2 Summary of vaginitis and cervicitis

	Normal findings	Bacterial vaginosis	Vulvovaginal candidiasis	Trichomoniasis	Cervicitis
Etiology	–	*Gardnerella vaginalis, Prevotella*, *Megasphaera*, *Mobiluncus,* and anaerobes	*Candida albicans*, non-albicans *Candida* species	*Trichomonas vaginalis*	*Neisseria gonorrhoeae*, *Chlamydia trachomatis*, *Mycoplasma genitalium*
Symptom presentation	Clear, white vaginal discharge	Fishy odor, discharge, pruritus	Pruritus, discomfort, dysuria, discharge	Vaginal discharge, pain with intercourse, dysuria, can be asymptomatic	Purulent vaginal discharge, lower abdominal discomfort, dysuria
Physical exam findings	Vaginal pH 3.8 4.2 Negative KOH "whiff" test	Malodorous "fishy," milky white vaginal discharge Vaginal pH > 4.5 Positive KOH "whiff" test	Thick, white "cottage cheese" vaginal discharge Vaginal inflammation and erythema Vaginal pH < 4.5	Malodorous, frothy, gray, or yellow-green vaginal discharge Vaginal pH > 4.5 KOH "whiff" test can be positive Cervical petechiae or "strawberry cervix"	Endocervical purulent secretions Cervical motion tenderness Negative KOH "whiff" test
Wet mount findings	Lactobacilli on wet mount	"Clue cells" on wet mount with no/few WBCs and decreased lactobacilli	Possible pseudohyphae on wet mount with few to many WBCs	Many WBCs and motile, flagellated protozoa on wet mount	Many WBCs on wet mount, possible intracellular cocci in *N. gonorrhoeae* infection

metronidazole 500 mg twice daily can be prescribed but has no advantage over the single-dose regimen for initial treatment in HIV-uninfected women [2]. The recommended treatment regimen for HIV-infected women is oral metronidazole 500 mg twice daily for 7 days [18]. All sexual partners should also undergo treatment [2]. If the first-line or alternative treatment regimens fail, a 7-day course of oral metronidazole or tinidazole in a daily 2-gram dose is recommended [2]. Alcohol consumption should be avoided during treatment with nitroimidazoles [18]. Up to 10% of clinical *Trichomonas vaginalis* isolates may be resistant to metronidazole and 1% resistant to tinidazole [18]. In recurrent disease or suspected treatment failure, sensitivity testing should be pursued [18]. Studies have shown that resistance can be overcome with higher doses of oral metronidazole or tinidazole along with intravaginal therapy [2]. For patients who do not respond to nitroimidazole treatments, consultation with an infectious diseases specialist is recommended [18] (Table 5.1). Trichomoniasis in pregnant women is associated with adverse outcomes including preterm birth, premature ruptures of membranes, and delivery of low birthweight infant [18]. All pregnant women who are diagnosed with trichomoniasis should undergo treatment and be counseled on partner treatment and condom use for prevention of sexually transmitted diseases [18].

Non-infectious Causes of Vaginitis

Foreign Body

Foreign bodies in the vagina can cause inflammation leading to foul-smelling and profuse discharge. The most common vaginal foreign body is toilet paper [28] though retained tampons can also be a cause in adolescent women [29]. Removal of the foreign body is definitive treatment.

Vulvar Vestibulitis

Vestibulitis is caused by the contact between acidic vaginal secretions and abnormal vestibular tissue which results in burning discomfort and dyspareunia [2]. Examination reveals erythematous, focal, tender lesions in the vestibule adjacent to the hymen. Symptomatic treatment includes avoidance of possible allergens and topical corticosteroids [2].

Allergic Vaginitis

Irritant contact and allergic dermatitis are non-infectious etiologies of vaginitis commonly associated with feminine hygiene products, contraceptives, and other causes [5]. Diagnosis can be confirmed by resolution of symptoms after discontinuation of the offending agent [29].

Cervicitis

Epidemiology

Cervicitis can be either infectious or non-infectious in etiology. Endocervical cervicitis is often infectious and caused by *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, or possibly *Mycoplasma genitalium*. Cervicitis can accompany trichomoniasis, genital herpes (particularly HSV-2 infection), and even BV. Risk factors for infectious cervicitis include age < 25 years old, having a new sexual partner or sex partner with concurrent partners, or an STI [18]. Ectocervical cervicitis is typically non-infectious and can be caused by idiopathic inflammation of the ectropion or chemical irritants [2].

Diagnosis

Purulent vaginal discharge is the primary symptom of women with cervicitis [2]. This may be accompanied by dysuria, abnormal uterine bleeding, lower abdominal pain, or dyspareunia. In non-infectious cervicitis, postcoital bleeding can occur due to an inflamed ectropion [2]. Leukorrhea (>10 WBC per high power field) on microscopy of the cervicovaginal fluid is often associated with chlamydia and gonorrhea infections of the cervix [18] (Fig. 5.2). Gram stain is not a sensitive indicator of infection in women [18], but the presence of intracellular gram-negative cocci can be specific for gonococcal infection [2]. Vaginal pH may also be elevated in the setting of cervicitis. Adolescent women with cervicitis should be evaluated for pelvic inflammatory disease (PID) and should be tested for gonorrhea and chlamydia infection with NAAT on either vaginal, cervical, or urine samples [18]. Microscopy, culture, and NAAT are useful diagnostic tools to evaluate for *Trichomonas vaginalis* as an etiology. The utility of specific testing for HSV-2 is unknown, though PCR, culture, and serologic testing can be considered, particularly if characteristic ulcerative lesions are noted [18]. All adolescents with concern for an STI should undergo testing for HIV and syphilis [18].

Treatment

For women at risk of STI with a presentation consistent with infectious cervicitis, empiric therapy for *Neisseria gonorrhoeae* or *Chlamydia trachomatis* should be strongly considered with either oral azithromycin 1 gm once or oral doxycycline 100 mg twice daily for 7 days and additional gonococcal-specific therapy in women at high risk or in areas with high gonorrhea prevalence (Table 5.1). Alternatively, for patients at lower risk or with good follow-up, diagnostic testing can guide pathogen-specific treatment regimens. For gonorrhea infection, primary treatment should include ceftriaxone 250 mg intramuscular with oral azithromycin 1 gm once under

direct observation. For chlamydia infection, oral doxycycline 100 mg twice daily for 7 days is an alternative to azithromycin [18]. If an STI is suspected or identified, all male or female sexual partners in the past 60 days should be referred for evaluation, testing, and treatment [18]. Women with gonorrhea or chlamydia infections should be retested 3 months after completion of therapy due to high risk of reinfection. The pathogenic role of *Mycoplasma genitalium* in cervicitis is unclear [18], and the pathogen is difficult to diagnose due to limited availability of diagnostic tests. It may be considered cases of clinically significant cervicitis that persist after azithromycin or doxycycline therapy in which re-exposure to an infected partner or medical nonadherence is unlikely. Infection may be treated with doxycycline or azithromycin, though treatment failures (particularly with doxycycline) occur and may be treated with moxifloxacin 400 mg once daily for 7–14 days. Treatment of HSV should also be prescribed if characteristic lesions are visible or diagnostic testing confirms the diagnosis [18] (Table 5.1).

Pregnancy Considerations

Diagnosis and management of cervicitis in pregnant women varies by pathogen. Pregnant women with *Neisseria gonorrhoeae* infection should be treated with dual therapy consisting of ceftriaxone 250 mg intramuscular once and oral azithromycin 1 gm in a single dose. Doxycycline is contraindicated in the second and third trimesters of pregnancy, and fluoroquinolones should also generally be avoided. Azithromycin is safe and effective; alternative treatment regimens for *Chlamydia trachomatis* infection include oral amoxicillin 500 mg three times daily for 7 days and oral erythromycin 500 mg four times daily for 7 days. Test of cure to document eradication should be performed 3–4 weeks after completion of therapy due to severe sequelae to mothers and neonates if infection persists.

Case Conclusion

Anna is evaluated for vaginitis. Her complaints of thin secretions with “fishy” odor and physical examination including microscopy with “clue cells” and elevated vaginal pH are consistent with the diagnosis of BV. Given her history of unprotected sexual intercourse, she was evaluated for STIs, including chlamydia, gonorrhea, HIV, and syphilis. A speculum examination with vaginal fluid sampling was helpful in establishing a diagnosis and ruling out retained foreign body. A pregnancy test was negative. She underwent counseling on using condoms to protect herself from unwanted pregnancy and STIs (sexually transmitted infections). She also received counseling regarding smoking cessation and vaginal health practices, such as avoiding douching, in order to prevent recurrence risk.

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Chapter 6
Pelvic Inflammatory Disease

Donald E. Greydanus, Kevin W. Cates, and Nina Sadigh

Case Study
A 17-year-old female comes in to see her clinician for an acute care visit. Her chief complaint is of a constant lower abdominal pain that began approximately 4 days ago. The patient notes she has been sexually active for the last 6 months with several different partners. Depending on the partner, she will use condoms for birth control, but will not if her partner does not want to use them. She states that recently she has noted some thick vaginal discharge and pain with urination as well.

She has a pulse of 110 with a temperature of 38.5 °C; other vital signs are stable. The rest of her physical examination reveals a diffusely tender lower abdomen with decreased bowel sounds and rebound tenderness. The pelvic examination demonstrates purulent vaginal discharge, cervical motion tenderness, and a friable-appearing cervix along with bilateral adnexal tenderness. A wet mount of vaginal fluid shows a significant number of WBCs, and a urine pregnancy test is negative. Endocervical swabs for *Chlamydia trachomatis* and *Neisseria gonorrhoeae* are obtained using nucleic acid amplification test (NAAT) methodology.

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A diagnosis of pelvic inflammatory disease is made, and initial treatment is with ceftriaxone 250 mg intramuscularly in a single dose with probenecid 1 g orally and doxycycline 100 mg orally twice a day for 14 days. She will see her physician in 3 days for a follow-up evaluation or sooner if she becomes worse.

Syndrome Description

Pelvic inflammatory disease (PID) is a polymicrobial infection of the female upper genital tract that typically is caused by *Neisseria gonorrhoeae* and/or *Chlamydia trachomatis* by way of sexual transmission but often involves a variety of other microbes as well that are classically part of the vagino-cervical endogenous flora (Table 6.1) [1, 2]. *C. trachomatis*-induced PID is more common in younger females (i.e., 16–24 years of age) vs older females [3].

Classically, a cervical infection occurs before the overt PID symptomatology. *N. gonorrhoeae* is found in 25–50% of PID cases, while *C. trachomatis* is noted in 10–43%; additional bacteria (i.e., anaerobic and facultative bacteria) are identified in 30% or more [2]. Pelvic inflammatory disease (PID) is an ascending infection that initiates in the cervix and vagina and moves to the upper genital tract and can involve various combinations of acute salpingitis, endometritis, tubo-ovarian abscess, oophoritis, pelvic peritonitis, and/or perihepatitis [1, 2, 4, 5].

About one million cases of PID are diagnosed annually in the United States, with about one-third occurring in adolescents. These figures are imprecise due to a lack of robust surveillance data, complicated by missed or unreported cases, regional

Table 6.1 Microbes found in pelvic inflammatory disease

Chlamydia trachomatis
Neisseria gonorrhoeae
Gardnerella vaginalis
Haemophilus influenzae
Bacteroides species (*B. fragilis, B. bivius*, *B. disiens*)
Mycoplasma genitalium
Group B streptococcus (*S. agalactiae*)
Coliforms (*Enterobacteriaceae*)
Peptostreptococcus
Streptococcus faecalis
Ureaplasma urealyticum
Neisseria meningitides
Mycoplasma hominis
Enterococcus
Cytomegalovirus
Other anaerobes

surveillance differences, and the clinical difficulty in differentiating between PID and cervicitis [1]. Thus, PID remains a serious health concern in adolescents, though the prevalence of PID and associated microbial infections may rise or fall over time [6–8].

Risk Factors

A number of risk factors are found with PID as noted in Table 6.2 [1, 9]. The highest prevalence of PID is in young adolescent females 15–19 years of age who begin coital behavior early, have multiple sex partners, and do not use condoms consistently [10]. The young adolescent female has an immature cervix with a transitional zone of columnar epithelium which provides a favorable place for growth of *C. trachomatis* and *N. gonorrhoeae* in contrast to squamous epithelium of older females [1, 2].

Immune System and PID

Also immature is the young adolescent immune system in which the antibody and CD4+ T cell responses are sometimes insufficient to remove the presence of *C. trachomatis* which can develop as a silent infection [11]. Such an infection can result in stimulation of the innate immune receptor with Toll-like receptor 1, CD4+ T cell responses, anti-*C. trachomatis* antibodies (i.e., 60-kDa heat shock protein), and TH1 as well as TH17 immune responses that leads to inflammation and eventually chronic injury to the genital tract [12, 13]. Research continues into understanding cell-autonomous immunity in response to *C. trachomatis* infection [14].

Fallopian tube damage from infection with *N. gonorrhoeae* can result from release of lytic transglycosylases (LTs) (particularly LtgA and LtgD) that leads to

Table 6.2 PID risk factors

Adolescence
Young adulthood
Adolescent cervical ectropion
Coital behavior with absent or minimal condom use
Multiple sex partners
Coitus during menstruation
History of contraception (non-barrier)
New intrauterine device insertion
Immature immune system
History PID
History of bacterial vaginosis
Vaginal douching

development and release of peptidoglycans with a large inflammatory response, impairment of lysozyme/neutrophil action, and resultant fallopian tube cell damage [15–17]. Repeated *C. trachomatis* infection can lead to more fallopian tube cell damage. The role of telocytes (type of interstitial or stromal cell) in PID-induced damage is under research [18]. *C. trachomatis* immunopathology is so profound that one proposed method of nonsurgical, irreversible contraception in adult females is to induce tube fibrosis through carefully controlled *C. trachomatis* infection [19].

IUD and PID

A potential link between intrauterine devices (IUDs) and PID has been controversial for the past half-century [1, 20]. Multifilament IUD tail strings have been implicated as the cause of increased infections seen in some studies, providing a site for bacterial colonization which was not subjected to the immunologic regulation of the cervical and uterine epithelia, thereby facilitating infection [20]. Current research suggests that IUDs that are inserted now which use monofilament tail strings pose a low PID risk in adolescents (nulliparous or parous) and no more than seen with adult females [21–23]. An adolescent female who receives an IUD should be screened for *N. gonorrhoeae* and *C. trachomatis* as per their risk factors and also at the time of IUD insertion [22, 24].

PID Symptomatology

Females with PID may present with a variety of symptoms that range from no or minimal symptoms to vaginal bleeding, vaginal/cervical discharge, abdominal pain (lower and/or right upper quadrant; pelvic pain), postcoital bleeding, urinary frequency, dysuria, fever, chills, dyspareunia, and/or variable gastrointestinal symptoms (i.e., nausea, emesis, diarrhea, constipation) [1, 2]. The classic PID presentation is vaginal (cervical) discharge with lower abdominal or pelvic pain. Research noted that 13% of patients with PID that were studied using endometrial samples had subclinical PID [25, 26].

Approximately 4% (3–10%) of females with PID also have perihepatitis (Fitz-Hugh–Curtis syndrome) in which paracolic gutter spread of the lower genital tract infection/inflammation leads to inflammation of the fibrous liver (Glisson's) capsule and local peritoneum; there can be fever, nausea, emesis, right upper quadrant pain, right pleural effusion, and/or right shoulder pain [27–38]. The presence of right upper quadrant pain in a sexually active female should raise suspicion for this possibility.

Normal and Abnormal Physical Examination

Depending on the specific PID presentation, the abdominal examination can vary, but the classic PID presentation is that of lower quadrant tenderness in association with cervical discharge. There may be an acute abdomen with rebound tenderness and decreased bowel sounds. If perihepatitis is present, there may be right upper quadrant tenderness with absence of lower abdominal pain. A pelvic examination may reveal cervical motion tenderness with or without uterine or adnexal tenderness.

The Centers for Disease Control and Prevention's 2015 STD Treatment Guidelines note that minimal clinical criteria for PID include one or more cervical motion tenderness, uterine tenderness, and/or adnexal tenderness (Table 6.3) [39]. Table 6.3 also lists additional CDC criteria for the diagnosis of PID to support the minimal criteria and also lists the most specific CDC PID criteria that involves endometrial biopsy, transvaginal sonography, magnetic resonance imaging, or laparoscopy [39].

Clinical findings can have an 87% sensitivity versus 50% specificity in contrast to laparoscopy (81% sensitivity versus 100% specificity), transvaginal ultrasound (30% sensitivity versus 67% specificity), endometrial biopsy (74% sensitivity versus 84% specificity), and endometrial culture (83% sensitivity versus 26% specificity) [1, 2, 40]. The role of imaging in the diagnosis and differential diagnosis of PID remains under study [32, 33, 40]. Increased serum procalcitonin levels are found in those with tubo-ovarian abscess (TOA) and can be useful as a TOA marker [41].

Table 6.3 Diagnostic criteria for PID (2015 CDC STD guidelines) [39]

1. *Minimal criteria (one or more)*
(a) Cervical motion tenderness
(b) Uterine tenderness
(c) Adnexal tenderness
2. *Additional criteria (one or more to support minimal criteria for PID)*
(a) Oral temperature over 101 degrees F (over 38.3 degrees C)
(b) Abnormal cervical mucopurulent discharge or cervical friability
(c) Presence of abundant numbers of WBC on saline microscopy of vaginal fluid
(d) Elevated erythrocyte sedimentation rate
(e) Elevated C-reactive protein
(f) Laboratory documentation of cervical infection with *N. gonorrhoeae* or *C. trachomatis*
3. *Specific criteria*
(a) Positive biopsy of endometrium showing endometritis
(b) Evidence of PID on laparoscopy
(c) Ultrasound (transvaginal) or MRI shows fallopian tubes that are thick and filled with fluid; may be free fluid in the pelvis or a tubo-ovarian complex; or Doppler studies suggest pelvic infection via tubal hyperemia

Differential Diagnosis

It can be difficult to accurately diagnose PID since the symptomatology can vary considerably, and it may be challenging to obtain a complete or accurate history from a young, anxious adolescent who may be in distressing pain. PID may be silent or present with minimal symptoms and thus be missed. If the cervical discharge appears normal (i.e., is not mucopurulent) and a saline preparation of vaginal fluid does not reveal white blood cells, the clinician should carefully consider other causes of the abdominal pain (Table 6.4). The differential diagnosis is extensive and

Table 6.4 Differential diagnosis of pelvic inflammatory disease

Acute intermittent porphyria
Adnexal torsion
Appendicitis
Constipation
Cystitis (urinary tract infection)
Diverticulitis
Dysmenorrhea
Endometriosis
Ectopic pregnancy
Fallopian tube torsion
Functional abdominal pain
Gastroenteritis (as due to *Yersinia enterocolitica* or *Campylobacter fetus*)
Genital trauma
Henoch-Schonlein syndrome
Hemolytic-uremic syndrome
Inflammatory bowel disease
Irritable bowel disease
Lead intoxication
Lupus serositis
Meckel's diverticulum
Mesenteric lymphadenitis
Mesenteric vascular disease
Ovarian cyst (with or without torsion or rupture)
Ovarian neoplasm (including teratoma rupture)
Ovulation (Mittelschmerz)
Pelvic adhesions
Pregnancy complication
Pyelonephritis
Reiter's syndrome
Septic abortion
Sickle cell crisis
Urethritis
Ureterocele
Urolithiasis
Others

Used with permission and modified from Greydanus et al. [42]

can lead to investigation of various systems including gynecologic, genitourologic, gastrointestinal, hematologic, rheumatologic, and others [42]. Also complicating the PID picture is that it may rarely occur in females without any history of sexual activity [43–46].

Treatment

An early diagnosis following the 2015 CDC guidelines is important in the management of PID; this should be followed by choosing an antibiotic regimen recommended by the 2015 guidelines as well [39] (Table 6.5). Acceptable improvement is seen in 2–3 days with absence of fever, considerable reduction in abdominal tenderness (rebound), and considerable lessening in motion tenderness of the cervix, uterus, and adnexal areas [39]. An iatric-based problem in reducing the devastation of PID is that physicians do not always follow these recommended diagnostic and management guidelines; care may vary depending on clinician specialty [47–52].

These management regimens provide polymicrobial antibiotic coverage that is intended to treat *Neisseria gonorrhoeae, Chlamydia trachomatis, Mycoplasma genitalium*, and other facultative as well as anaerobic bacteria that may be present [1]. IV doxycycline is painful and oral administration is preferred if tolerated. Other IV antibiotics may be stopped in 24 hours if there is acceptable improvement, and oral doxycycline is continued for a total of 14 days. Moxifloxacin (400 mg once a day for 14 days) can be as effective as ofloxacin with metronidazole in uncomplicated disease [53–55].

Guidelines do change over time as seen with the removal of a quinolone agent because of a significant increase in gonococcal resistance – QRNG (quinolone-resistant *N. gonorrhoeae*) – as well as decreasing susceptibility to third-generation cephalosporins [1, 56]. Also complicating this picture is that twenty-first-century human beings are highly mobile – leading to changes in prev-

Table 6.5 Antibiotic management of PID (2015 CDC STD guidelines) [39]

ORAL/IM
Ceftriaxone 250 mg IM in a single dose OR cefoxitin 2 g IM in a single dose and probenecid 1 g orally concurrently OR other parenteral third-generation cephalosporin (as ceftizoxime or cefotaxime)
PLUS
Doxycycline 100 mg orally twice a day for 14 days with or without metronidazole 500 mg orally twice a day for 14 days
PARENTERAL
Regimen A
Cefotetan 2 g IV every 12 hours OR cefoxitin 2 g IV every 6 hours PLUS doxycycline 100 mg orally or IV every 12 hours
Regimen B
Clindamycin 900 mg IV every 8 hours PLUS gentamicin loading dose IV or IM (2 mg/kg body weight) followed by a maintenance dose (1.5 mg/kg) every 8 hours. Single daily dosing (3–5 mg/kg) can be substituted
Alternative parental regimen
Ampicillin/sulbactam 3 g IV every 6 hours plus doxycycline 100 mg orally or IV every 12 hours

alence and antibiotic resistance as in such bacteria as *Ureaplasma urealyticum* and *Mycoplasma genitalium* [36, 57–59].

The oral/IM or parenteral (IV) regimens are equally effective in managing mild to moderate PID. However, some patients do not improve and careful re-evaluation of the initial PID management plan should occur in 48–72 hours to see if the initial treatment is effective. Indications for hospitalized management include high fever, inability to follow up the outpatient regimen, intolerable nausea/emesis, immediate loss of medication due to emesis, pregnancy, and presence of a surgical emergency (i.e., appendicitis, others) [1, 2]. If a tubo-ovarian abscess (TOA) is present or suspected, hospitalization along with imaging is needed; antibiotics are needed to cover for anaerobic bacteria along with surgery (i.e., abscess drainage) [60]. Complicating the hospital management in the twenty-first century can be administrative concerns with cost of treatment [61].

Consultation with infectious disease consultants may be needed in refractory situations. PID can develop more rapidly and/or more subtly than appreciated by the evaluating clinician [1]. Third-generation cephalosporins are limited in their coverage of anaerobic bacteria, and thus, metronidazole is important to use which will also treat potentially concomitant bacterial vaginosis [39]. Treatment can be tailored to antibiotic sensitivity testing if available.

Identifying and treating subclinical PID remains a challenge for clinicians in preventing PID sequelae that may occur in 25% after the first PID episode [26, 62]. These complications include chronic pelvic pain, ectopic pregnancy, and infertility due to tubal scarring and adhesions [1, 2, 18]. Weström's classic work noted that 16.0% of patients with PID identified by laparoscopy developed infertility versus 2.7% infertility in the control group [63]. In this study 9.1% of the first pregnancy after the PID were ectopic pregnancies versus 1.4% of the controls [63].

Persons with PID should also be tested for HIV as well as potentially for other sexually transmitted diseases. Sex partners of a female with PID should be evaluated and typically are treated for *N. gonorrhoeae and C. trachomatis*. The CDC recommends treatment of these sex partners within the past 60 days of the PID diagnosis even though most of the male sex partners may be asymptomatic [2, 39]. If the sex partner was over 60 days from the PID diagnosis, screen/treat the most recent sex partner. Principles of EPT (expedited partner therapy) can be followed [39]. Sexual behavior is not recommended until both the patient and sex partner (s) are adequately treated [39]. The PID patient should be seen again within 3–6 months of the PID treatment. Education about PID is important including that it can occur again and that sexually transmitted diseases can be asymptomatic.

Prevention

Screening Programs

The acute manifestations and the chronic complications of PID in females necessitate a consummate preventive stratagem involving healthcare clinicians and the public health sector. Screening programs for *Chlamydia trachomatis* have been

augmented over the past three decades in attempts to lower PID incidence, and the US Preventive Services Task Force (USPSTF) currently recommends *C. trachomatis* annual screening of all sexually active females under 26 years of age [64]. A screening method typically well-received by female patients is the "self-taken swab" in which a swab done by the patient can receive nucleic acid amplification analysis for detection of both *C. trachomatis* and *N. gonorrhoeae* [65–67].

Screening programs, including urine collection technology for both females and males, may lower PID prevalence if done properly.

The prevention of individual cases of PID is a *direct* effect seen by strategically combining aggressive screening with treatment of identified infections; also, an *indirect* effect may be seen via lowering rates of inimical bacterial transmission [68, 69]. One study reported a 56% reduction in PID incidence in 18–34-year-old females receiving proper chlamydia screening; this reduction was in contrast to those not involved in this screening program [70].

Other *C. trachomatis* screening programs demonstrate success in lowering PID in adolescents but also reveal that such benefits can be limited if inadequate or suboptimal screening policies are in effect [71]. Screening programs are not effective if the public health policies behind these programs are limited and if healthcare clinicians are not motivated to maximize the benefit of these policies [1]. The cost of such programs may be of concern to some who fail to understand the benefit of overall PID prevention in contrast to the benefit of a single screening tool [72]. Policy makers in various countries may raise concerns with cost-effectiveness and data validity of such screening program with the result that implementation of such screening varies from country to country and, thus, STD data comparison becomes complicated if not impossible [1, 73].

Education

Other complex but potentially effective methods of PID prevention would include delaying the onset of adolescent coital behavior and educating youth to the disease-preventive effects of regular condom use [74–76]. Comprehensive and continual sexual education is an important public health tool which should include information about obtaining condoms, using them in the most effective manner, and about the importance of incorporating regular screening for sexually transmitted infections into the healthcare of sexually active adolescents.

Public health officials and society should weigh the cost of condoms with the cost of PID (i.e., diagnosis and management) [77, 78]. Specific education of sexually active females about lower abdominal pain as an indication for seeking proper medical management is an important strategy in PID prevention [79]. Public health education about STDs, STD prevention, and PID should occur not just in schools but also in the clinician's office.

Unfortunately some clinicians are providing limited sexuality education as well as suboptimal STD screening for adolescents due to a variety of reasons including concerns with confidentiality and local as well as national community influences [76, 77]. Failure to provide aggressive STD screening, implement established PID

treatment protocols, utilize guidance from local as well as national susceptibility surveillance, and provide regular PID follow-up only encourages an increased prevalence of acute and recurrent PID in adolescents including those at high risk such as those incarcerated, runaways, and others [1, 78–85].

Other Prevention Strategies

Improved prevention programs also depend on research to elucidate the complexities of the immune system and how these organisms implicated in sexually transmitted diseases can overcome immunologic defenses [13–18]. Additional research is needed to establish the actual effects of various STD screening tools, to clarify results of conflicting STD research, and to provide guidance in reaching high-risk populations [86–88]. Another powerful but likely controversial tool in this stratagem would be the development of an effective vaccine for STDs including *C. trachomatis* and *N. gonorrhoeae* [1, 11, 67, 89–96].

Other Considerations

As noted careful follow-up of females with a diagnosis of pelvic inflammatory disease is needed to seek rapid improvement and minimize complications such as infertility and chronic abdominal pain as well as increased risk for ectopic pregnancy [97]. Data suggest that young minority females have disproportionately high rates of PID complications [98]. Females with PID who are pregnant should be hospitalized for intravenous antibiotic treatment as they are at increased risk for preterm delivery and maternal morbidity [39].

Current studies conclude that adolescent and adult females with an IUD (copper or other nonhormonal types) have a low risk for PID; those receiving an IUD should be screened for the presence of *N. gonorrhoeae* and *C. trachomatis* [22–24, 39, 99–101]. Keeping or removing the IUD (copper or other nonhormonal types) when PID is present does not seem to change the outcome [39]. However, if an adolescent female has an IUD and treatment for PID does not result in significant improvement in 48–72 hours, some clinicians will remove the IUD [39].

HIV and PID

The presence of HIV in a female with an IUD and PID does not seem to increase PID complications nor the difficulty of PID management [102]. Females with PID should be screened for HIV, evaluated for the potential of being involved in abusive and/or exploitive sex, and advised to use condoms to reduce STD risks [98, 103].

Treatment of adolescent or young adult females with PID and HIV is the same as for PID in general [39]. Some tentative data suggest the possibility that those with both PID and HIV may have increased risk for tubo-ovarian abscess as well as for concomitant infection with streptococcal and *Mycoplasma hominis* infections [39].

Incarceration

Incarcerated adolescents are affected by an increased incidence of PID and markedly elevated rates of *N. gonorrhoeae* and *C. trachomatis* at admission, suggesting that intensive screening and intervention in this population may have a disproportionately critical public impact [104]. Further, this may propose that public health interventions in youth at risk of incarceration or those previously incarcerated may be similarly effective, due to the persistence of risk factors in these populations.

Lesbian, Bisexual, and Transgender Youth

Lesbian, bisexual, and transgender adolescents may be less likely to seek healthcare for sexual concerns or may be less likely to identify their sexual activity as relevant to a health concern even when they are engaging in behaviors which may increase their risk for STDs and PID [105]. Lesbian and bisexual adolescent females may still engage in sexual activity that could put them at risk for PID and should not be assumed to have no or low risk of PID on the basis of their sexual identity [105, 106].

Transgender and gender-nonconforming youth may have a gender presentation which discourages the clinician from considering PID, e.g., if assigned female sex at birth, but presenting as male. Transgender or gender-nonconforming youth may also deny terminology that is incongruent with their gender identity, e.g., denying "vaginal sex" because, although an anatomically accurate description, the terminology may be distressing to this youth. In these situations, a clinician must be prepared to pursue a careful and thorough history while working to build rapport with the patient by affirming their gender and/or sexual identify.

Sexual Violence

Patients who have experienced rape or sexual violence may be reluctant to seek care, may delay care, or may view examination and intervention as an additional intrusion [107]. Because of this, identification and treatment of STDs and PID may be challenging in such a patient. The psychological impact of sexual violence may require additional caution on the part of the clinician, with support from allied

health professionals and rape crisis programs potentially providing the support necessary for such a patient to accept care, examination, and treatment if necessary [107].

Other PID Correlations

Adolescents may be more likely than adults to experience PID recurrence within the first 30 days and may require closer follow-up [108]. PID is also a known risk factor for chronic pelvic pain as well as ectopic pregnancy and tubal infertility, with a higher frequency and severity of PID episodes associated with greater risk [12, 18, 109–111].

Recent studies have examined potential correlations between PID and gynecologic cancers, such as endometrial and ovarian cancer [112, 113]. A population-based study in Taiwan found a higher risk of ovarian cancer in patients with PID, but did not delineate whether PID itself or risk factors related to PID (i.e., infertility, no history of oral contraceptive use) contributed to the higher risk of ovarian cancer [112]. Adults with a history of PID and cervical cancer have an increased risk for a second primary malignancy in the genitals, bladder, and colon [114].

Case Conclusion

The patient's presentation is consistent with pelvic inflammatory disease given her history of unprotected coital behavior with clinical symptoms of abdominal pain and dysuria, laboratory findings of elevated WBC count on saline microscopy of vaginal fluid, as well as examination findings of abnormal vaginal discharge, cervical motion tenderness, and bilateral adnexal tenderness.

The clinician should begin antibiotics immediately, in this case with intramuscular ceftriaxone and oral doxycycline with or without metronidazole. This should lead to improvement seen in 2–3 days with absence of fever and significant reduction in both abdominal tenderness and motion tenderness of the cervix, uterus, and adnexal areas. Refractory pelvic inflammatory disease may require hospitalization and/or consultation with infectious disease specialists.

The physician should also test the patient for HIV as well as other STDs. Sexual partners of the patient should also evaluated for *N. gonorrhoeae* and *C. trachomatis*. The physician should educate the patient regarding prevention of PID, including that recurrence is a possibility. Clinicians should remain vigilant in improving the awareness, prevention, and management of this common and potentially devastating sexually transmitted disease [98].

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Chapter 7
Urethritis

Karen Simpson and Brandii Criss

Case Study

A 17-year-old male patient presents with a 3-day history of burning with urination. He has also noticed what he describes as a "clear-to-whitish" discharge coming from his penis. He denies urinary urgency or frequency. He has no testicular or scrotal pain and denies fevers or other constitutional symptoms.

On psychosocial screening, the patient reports sexarche at 15 years of age with female partners only. He reports present sexual activity with one female partner for the past 4 months with condom use "most of the time." He does report a prior history of sexually transmitted infection (STI) approximately 7 months ago. Patient reports that he is not sure which infection it was and knows only that he was treated with a "shot and some pills." He does not know if his partner at that time was treated. He reports no significant past medical history and has no known history of urinary tract infections or anatomic abnormalities of the urinary tract. He reports no allergies to medications.

Physical examination reveals a young male, who appears his stated age; he is afebrile with stable vital signs. His genitourinary examination is significant for a cloudy urethral discharge that patient expressed from his penis. He has no skin lesions in his genital region, his testicles are without swelling or tenderness, and there is no significant lymphadenopathy or tenderness in the inguinal region.

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Investigations include a urine dipstick (point of care) which was normal except for trace leukocyte esterase. His urine is sent for gonorrhea, chlamydia, and trichomonas nucleic acid amplification tests (NAAT); human immunodeficiency virus (HIV) and syphilis tests were also performed.

Questions

1. What is the most likely etiologic organism for the patient's symptoms?
2. What laboratory investigations, if any, would you perform?
3. Discuss the presumptive treatment options for urethritis due to sexually transmitted infection.
4. How should this patient and his sexual partner(s) be counseled?

Syndrome Description

Urethritis, as its name suggests, refers to inflammation of the urethra. Although women can technically have urethral inflammation related to STIs, urethritis is more commonly thought of as a male syndrome. Symptoms of urethritis may include dysuria, urinary urgency, urethral discomfort, and/or discharge [1]. Urethral discharge, when present, may be mucoid, mucopurulent, or purulent. Importantly, however, urethritis can also be asymptomatic [1].

Normal and Abnormal Physical Examination

General physical examination is usually normal; systemic syndromes accompanied by urethritis are not common in the young male patient. Abnormal examination may be confined to the genitourinary system. Small or shotty inguinal lymphadenopathy may be present and can be either tender or non-tender. The skin of the penis is generally normal, as is the testicular examination. Tenderness of the epididymis would raise concerns for epididymitis in addition to urethritis. Urethral discharge may be readily apparent. In other cases, elicitation of discharge may require expressing urethral contents by compressing the penis. For patient comfort, it is generally recommended that the patient, and not the examiner, perform this compression.

Some general signs that may help with narrowing the differential diagnosis are listed in Table 7.1 and discussed below.

Differential Diagnosis

The differential diagnosis of urethritis in the adolescent includes both infectious and noninfectious causes; see Table 7.1. The history and physical play important roles in determining the next steps in management. Point-of-care (POC) tests, when

available, can provide additional preliminary or diagnostic information to guide the therapeutic plan.

The most likely cause of acute urethritis in an adolescent is infectious – namely, STI or UTI. In the young male, STIs are by far the more common etiologic agents. Urinary tract infections (cystitis or pyelonephritis) may be the likely cause in the male with an abnormal genitourinary tract or who participates in insertive anal sexual intercourse. Urinary tract infections may be accompanied by any combination of dysuria, urgency, frequency, hematuria, and fever.

Urethritis resulting from a sexually transmitted infection is often classified as gonorrheal or non-gonorrheal urethritis (NGU) based on whether *N. gonorrhoeae* is the etiologic agent or not. Sexually transmitted infections should be considered in the sexually active young male or the male who has been sexually abused. Patients may also be asymptomatic. For a likely viral etiology, the patient may also present with symptoms of urethritis with or without other evidence of genital inflammation, vesicles, ulcers, or systemic symptoms e.g., fever or joint pain. Bacterial causes, including that due to Chlamydia and gonorrhea are by far the most commonly diagnosed etiologic agents. Gonorrhea which causes a more inflammatory response, is oftentimes symptomatic with a yellowish or green urethral discharge.

For cases of NGU, Chlamydia trachomatis is the most frequently diagnosed pathogen. Other not uncommon causes may include *Mycoplasma genitalium*, *Ureaplasma urealyticum*, *Trichomonas vaginalis*, and herpes simplex. Evaluation and treatment directed toward these additional agents tend to be done in cases where there is lack of, or inadequate response to appropriate first line therapy. The patient

Table 7.1 Physical examination signs supporting urethritis or suggestive of alternative diagnoses in patients with symptoms suggestive of urethritis

Signs	Likely differential
General	
Fever	Pyelonephritis, herpes
HEENT:	
Scleral injection	Behcet's, Stevens-Johnson syndrome (SJS), reactive arthritis
Oral ulcers	Behcet's, herpes stomatitis, SJS
Skin:	
Diffuse rash	SJS, herpes
Musculoskeletal:	
Joint pain/swelling	Reactive arthritis, SJS, Behcet's syndrome
Flank pain and hematuria	Renal stones
Genital:	
Ulcerations/vesicles	Herpes, SJS, Behcet's, herpes
Painful lesions	Herpes
Scant/watery discharge	Chlamydia, nonspecific
Purulent discharge	Gonorrhea, beta hemolytic strep, chlamydia, *M. genitalium*, *T. vaginalis*, *Candida albicans*
Green discharge	Gonorrhea

with HSV may also present with significant meatitis and/or herpetic lesions of the penis and/or systemic symptoms.

Age is an important differentiating factor in the epidemiology of urethritis. In general, STIs are more prevalent in the younger age groups (i.e., under age 35), whereas urinary tract pathogens (e.g., *Escherichia coli* [*E. coli*]) are more prevalent in older age groups. Of note, males who participate in insertive anal sexual intercourse may also be more likely to acquire *E. coli* urethritis regardless of age group.

Untreated, urethritis may progress to the development of epididymitis, epididymo-orchitis, or prostatitis. Chlamydia, gonorrhea, and *E. coli* tend to be the most common etiologic agents. Balanitis and balanoposthitis would present with local inflammatory changes of the glans penis and/or the foreskin. Urethritis may also be present as a part of a systemic disorder including Stevens-Johnson syndrome, Behcet's syndrome, and reactive athritis syndrome, and thus a general review of systems enquiry is important.

Noninfectious causes may also result in symptoms of urethritis. Potential factors may include trauma (including vigorous sexual practices, frequent masturbation, foreign body insertion, and "tucking"). The passage of renal stones may also cause urethral irritation as can dermatitis lesions. Finally, psychogenic etiology must be considered in the patient where the clinical evaluation and management are not consistent with the presenting urethral concerns.

Diagnosis

Urethritis is diagnosed based on the presence of clinical and/or laboratory evidence of urethral inflammation in the male. Diagnosis may be presumptive or definitive.

A presumptive diagnosis may be made in the sexually active patient presenting with symptoms or signs of urethritis – clear, mucoid, or mucopurulent urethral discharge with or without laboratory evidence of inflammation. Definitive diagnostic criteria includes the aforementioned symptoms, as well as: first void urine specimen with positive leukocyte esterase on urinalysis or urine dipstick or the presence of $\geq$10 white blood cells (wbcs)/hpf on a spun specimen [2, 3] or gram staining of urethral secretions with $\geq$2 wbcs/oil immersion field [3]. If gonococcal infection is present, gram staining may show the presence of gram-negative intracellular diplococci [gnid] (gentian violet and methylene blue staining are also alternatives to gram staining in the presence of gonococcal infection, intracellular purple diplococci may be seen with methylene blue or gentian violet smear) [2, 3].

For "first-catch" urine specimen mentioned above, the first void of the morning is preferred. However, this is generally not feasible clinically. The patient is thus requested to collect urine from the beginning of the urinary stream, without cleaning the urethral meatus ("wiping the penis") preferably after at minimum 1 hour has passed since the last urinary void [2].

Definitive diagnosis of urethritis due to a STI is generally made on nucleic acid amplification (NAAT) testing or culture (much less frequently performed).

Whether or not point-of-care microscopy is positive, first-catch urine specimen should be sent for NAAT for chlamydia and gonorrhea. Chlamydia and gonorrhea are by far the most common causes of urethritis in the adolescent and young adult population. *M. genitalium* and *T. vaginalis* are two other potential causes – however, testing for these is not routinely performed in the initial evaluation of male urethritis – due in part to limitations in diagnostic capabilities. There are no US Food and Drug Administration (FDA)-approved NAAT testing methods for trichomoniasis in males. NAAT for *M. genitalium* testing is validated and available in some (though not many) institutions, but no FDA-approved tests are available. Nucleic acid amplification specimens may include urine or urethral swab (not commonly done now that urine for NAAT is readily available, is very sensitive, and is with noninvasive collection method). Unfortunately, the availability of laboratories has decreased the need for microscope proficiency in clinicians.

Treatment

An adolescent male presenting with symptoms and signs of urethritis should be treated presumptively for both *C. trachomatis* and *N. gonorrhoeae* – the most common etiologic agents for urethritis in this age group. Presumptive treatment involves ceftriaxone 250 mg intramuscularly with azithromycin 1 gram by mouth single dose or doxycycline 100 mg orally twice per day for 7 days. Presumptive and early treatment is often done. This increases access to therapy, reduces transmission of infection to sexual partner(s) and decreases chances for urethritis complications (e.g. epididymitis, prostatitis and reactive arthritis). Regimes involving single dosing are preferred. Clinic personnel should directly observe administration of single-dose regimens or the administration of the first dose of a multidose regimen.

Treatment regimens can also be divided into those targeting nongonococcal and gonococcal urethritis.

Nongonococcal Urethritis (NGU)

The most commonly diagnosed sexually transmitted pathogen is chlamydia. For chlamydia urethritis, the first-line treatment regime involves azithromycin 1 gram orally or doxycycline 100 mg twice per day for 7 days. Alternatively, other oral regimes include levofloxacin 500 mg or ofloxacin 300 mg twice per day for 7 days [3].

In practice, even for patients definitively diagnosed with NGU, most end up being treated for both gonorrheal and chlamydial infections. Depending on the prevalence of trichomoniasis in the population and or provider's preference, presumptive treatment for trichomonas with metronidazole 2 grams can also be considered.

Gonococcal Urethritis

Given the rising rates of antimicrobial resistance in *N. gonorrhoeae*, gonococcal urethritis should be treated with two active antimicrobial agents. Dual therapy serves to decrease the risk of developing drug resistance and also to increase the efficacy of treatment for the individual patient. Currently, the Centers for Disease Control and Prevention (CDC) recommends that ceftriaxone 250 mg intramuscularly plus azithromycin 1 gram by mouth be utilized in the treatment of gonorrhea urethritis. If the recommended regime is not available or patient has allergy or significant intolerance to the recommended regime, alternative regimes are listed below:

- Cefixime 400 mg plus azithromycin 1 gram – oral single-dose regimen
- Gemifloxacin 320 mg plus azithromycin 2 gram – oral single-dose regimen
- Gentamicin 240 mg intramuscularly plus azithromycin 2 grams – single-dose regimen

Due to the rapidly evolving resistance pattern of *N. gonorrhoeae*, the provider is encouraged to continually check the Centers for Disease Control and Prevention Sexually Transmitted Diseases Treatment Guidelines webpage for the most recent recommendations.

Of note, previous recommendations were for a test of cure, particularly for those treated with alternate regimens. At this time, a test of cure is no longer routinely recommended for persons treated with an alternate regimen. However, in the case of unresolved symptoms, practitioners may consider repeating NAAT testing after 1–2 weeks. At that time, a sample should be sent for culture and resistance testing as well (may require coordination with local health department and/or the CDC).

General Instructions to Patient

It is highly recommended that sexual partners over the last 2 months (or the last partner if no sexual intercourse in 2 months) should be evaluated and treated. Patients and partner(s) should avoid sexual intercourse until at least 7 days after completing treatment (of index patient and partner(s)) and symptom resolution for all parties. Partner therapy options should be discussed and can even be offered directly to the index patient. Ideally, all sexual partners should receive a medical

evaluation, and this should be given a very strong recommendation. Expedited partner therapy (EPT) may be offered to heterosexual partners of index patients with chlamydia and or gonorrhea infection [4]. If the partner is not likely to seek medical evaluation and treatment in a timely manner, cefixime and azithromycin (or a prescription) included in the EPT packet should be offered to the index patient for partner therapy. In addition to the medication and instructions in the EPT packet, the partner should seek additional medical care and evaluation. Expedited partner therapy should not be routinely offered to men who have sex with men (MSM) as there may be an increased chance of co-occuring STIs including HIV infection.

Follow-Up

Routine test of cure is not recommended after treatment. However, the adolescent and young adult population may be at higher risk of reinfection, and thus a test of reinfection for chlamydia and gonorrhea may be performed in 3–6 months.

Persistent or Recurring Symptoms Soon After Completing Therapy

If the patient received a single-dose treatment regimen (e.g., ceftriaxone 250 mg intramuscular plus azithromycin 1 g by mouth), symptoms should generally resolve within 1 week. Patients with unresolved symptoms should be re-evaluated. First, providers will need to confirm that the patient took the medications as instructed and that they were able to tolerate them. Providers should also confirm that partners were adequately treated and that patients avoided sexual intercourse for at least 7 days after the last person was treated. A mucoid discharge may also be seen in "tucking" (folding and taping the penis along the perineum) as a result of mechanical irritation and does not require antibiotic therapy.

Nongonococcal Urethritis

If the patient was compliant with and tolerated therapy, we recommend re-evaluating with point-of-care testing (urine analysis with microscopy), if feasible. Clinicians can also consider resending a sample for NAAT for gonorrhea and chlamydia, with the caveat that repeat positive results within a one week time frame may represent nonviable organisms and do not necessarily indicate treatment failure. Where available, clinicians can also consider testing for *M. genitalium* and/or *T. vaginalis* infection.

If there is objective evidence of nongonococcal urethritis, providers should re-treat with the prior regimen if they suspect noncompliance or repeat infection from an untreated partner.

If the patient is thought to be compliant with treatment and adequate abstinence from sexual activity during the immediate treatment period, then persistence of NGU may be due to *M genitalium*. If *M. genitalium* is suspected, the approach to therapy should include:

- Use of azithromycin 1 gram (if doxycycline therapy was used prior) OR azithromycin 500-mg dose followed by 250 mg daily for 4 days OR moxifloxacin 400 mg by mouth once per day for 7–14 days [5].

Trichomoniasis may also be suspected in cases of non-resolving NGU; providers may consider treating with metronidazole or tinidazole 2 grams orally as single-dose regimen. Herpes simplex virus (HSV) generally presents with severe dysuria and observable inflammation of the urethral meatus. Herpetic genital lesions may also be present. In these cases, particularly if patient has not had adequate clinical response to any of the above-recommended regimes, providers can consider treating for HSV with appropriate antiviral therapy. Finally, if the patient continues with complaints after re-treatment, chronic prostatitis or psychogenic causes should be considered, and referral to a urologist may be helpful.

Gonococcal Urethritis

During re-evaluation of persistent urethritis symptoms, if one is considering persistent gonorrhea urethritis, clinicians should repeat gonorrhea testing with a urethral culture (with antimicrobial susceptibility) plus a NAAT 7–14 days after treatment. Most of these cases may represent reinfection rather than resistance. As a result, suspected treatment failures should first be re-treated with ceftriaxone and azithromycin. In cases where true treatment failure is thought to be more likely, treatment with alternate regimens (i.e., oral gemifloxacin 320 mg plus azithromycin 2 grams OR gentamicin 240 mg intramuscularly plus azithromycin 2 grams orally) can be considered. At this point, providers will generally want to coordinate with the Centers for Disease Control and Prevention, local health departments, and/or infectious disease specialists to ensure appropriate resistance testing, treatment, and reporting.

Prevention

Barrier methods such as male and female condoms are the best strategies for preventing transmission of most of the organisms that cause urethritis. Where possible, abstinence, monogamy, and avoidance of serial sexual partners may also be useful.

Other Considerations

Young men who have sex with men and who participate in anal insertive sex may also have urethritis from gram-negative organisms. Fluroquinolones should be considered as treatment option early in management.

HIV-positive youth: The treatment regimens for those with HIV disease are the same as those without HIV disease. Of note, there is some research to suggest that concomitant STIs, including those that cause urethritis, can increase HIV transmission due to mucosal injury.

Case Conclusion

For this sexually active young man presenting with urethritis, the differential diagnosis includes infectious and noninfectious etiologies. The most likely cause in healthy males under age 35 years is sexually transmitted infection, with *C. trachomatis* being the most prevalent. Other more common etiologies include *N. gonorrhoeae*, *M. genitalium*, and *T. vaginalis*.

Initial laboratory investigations may include POC tests including urinalysis and gram staining which may provide evidence of inflammation. Nucleic acid amplification tests for gonorrhea and chlamydia should be performed. Testing for *M. genitalium* and *T. vaginalis* may also be performed, particularly in cases of persistent urethritis despite adequate treatment and abstinence from sexual intercourse.

Generally, the adolescent and young adult patient presenting with symptoms, signs or preliminary laboratory evidence of urethritis are treated at that initial clinic visit. Presumptive therapy generally targets gonorrhea and chlamydia infection, and ceftriaxone and azithromycin (or doxycycline) are initiated. This is often done as youth populations have a higher prevalence of chlamydia and gonorrhea compared to older men where urethritis tends to be from a urinary tract infection. Additionally, adolescents and young adults may have challenges with follow-up and/or access to therapy. Thus providers should ensure that their patients have access to therapy, facilitate partner evaluation and treatment, and encourage abstinence until infection has been cleared.

Urethritis may be asymptomatic. Thus providers may intermittently screen the asympotomatic sexually active adolescent and young adult male atleast annually. Patients with higher risk factors maybe screened more often. Urethritis due to STIs is more likely in patients with a partner with a known or suspected STI, a new sexual partner, multiple sexual partners, serial sexual partners, inconsistent or inadequate condom use, and/or involvement in transactional sex (sexual involvement in exchange for money or favors).

Urethritis may co-occur with other infections (e.g., HIV, syphilis) related to sexual intercourse. Thus, HIV and syphilis screening is recommended in the sexu-

ally active male suspected of or diagnosed with any STI syndrome including urethritis. Safer sex behaviors, including abstinence, should always be promoted. Providers should also share general educational resources about sexually transmitted infections, medical care rights of the minor, and locations for access to STI treatment.

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Chapter 8
Proctitis and Other Rectal Complaints

Stephanie Hackett and Andres Camacho-Gonzalez

Case Study
A 21-year-old African American male presents to his primary care provider for an acute care visit. He reports a white mucoid rectal discharge in his underwear over the last 2 days. The patient is sexually active with men only and is always the receptive partner. He reports four sexual partners over the last 6 months with intermittent condom use. The last sexual encounter was about 1 week ago, and the patient states they did not use condoms. Upon further questioning, the patient also reports he thinks he has hemorrhoids. He states that over the last month, he has noticed several "bumps" near his anus. He describes the lesions as flesh colored and states they aren't painful, but their presence makes him feel uncomfortable during sexual encounters. The patient denies any fever, weight loss, diarrhea, constipation, blood per rectum, or rectal pain.

On physical exam his vital signs are all within normal range. Head, neck, chest, and abdominal exam are all within normal limits. His genital exam reveals a circumcised penis with no discharge or lesions. Testicles are both palpated in the scrotal sac with no lesions or other abnormalities noted. Mild inguinal lymphadenopathy is palpated bilaterally. His rectum reveals five

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well-circumscribed verrucous lesions ranging in size from about 2 to 5 mm. No discharge was seen at the rectum; however, the patient demonstrates to you a white mucoid discharge in his underwear. No other lesions were noted, and the rectum has good tone.

Questions for Consideration

- What are the primary clinical manifestations of proctitis?
- What considerations should be made during the diagnostic evaluation?
- What treatment is indicated at this time?
- What follow-up is necessary, if any, for this patient?

Syndrome Description

Proctitis is a general term to describe inflammation of the anus and rectal mucosa, while proctocolitis describes when the inflammation extends more than 15 cm into the sigmoid colon [1, 2]. Proctitis may be characterized by a variety of clinical manifestations including rectal discharge, rectal bleeding, rectal pain, dyschezia, urgency, and/or tenesmus. Patients may also report symptoms of colitis such as diarrhea, abdominal pain, bloating, blood in their stool, and weight loss. The medical provider should consider a broad differential diagnosis depending on the age and clinical manifestations; however, in adolescents and young adults, sexually transmitted infections (STIs) should be at the top of the differential given that the highest rates of STIs occur in this age group [3]. Other associated rectal complaints may occur in tandem with proctitis symptoms such as anal condyloma, hemorrhoids, anal fissures, vesicles, or syphilitic chancres.

Normal and Abnormal Physical Exam

When assessing a patient with rectal complaints, it is important to do a complete physical exam. Abnormal findings in areas different from the perianal region may complement the findings in the rectum and aid in the formulation of a differential diagnosis. A detailed inspection of the throat, abdomen, lymph nodes, joints, skin, inguinal area, penis/vagina, testicles, and perianal region should be completed. Any pain, masses, lesions, rashes, or discharge should be noted [1, 2]. The rectal exam should include a visual inspection of the perianal skin, digital palpation of the rectum, and assessment of the neuromuscular function of the perineum [2, 4].

Evaluation of lesions of the rectum should include their size and location as it would correspond to the hours of the clock. During visual inspection the examiner can evaluate for the presence of anal fissures, ulcers, vesicles, skin tags, external

hemorrhoids, warts, discharge, and rectal prolapse. A differentiation of lesions originating from the perianal region versus those prolapsing from the anal canal should also be noted. Palpation of the region should always include the inguinal lymph nodes, with evaluation of their size, firmness, and distribution. During the digital palpation of the rectum, the examiner will use water-soluble gel in the index finger for lubrication. The finger is inserted gently into the rectum allowing the examiner to evaluate for the presence of masses, internal hemorrhoids, and ulcers as well as to measure the contraction of external anal sphincter and the perianal muscles. In men palpation of the prostate should also be performed evaluating its size, consistency, presence of nodules, and pain. It is important to perform the digital rectal exam after STI testing since standard lubricants can be bacteriostatic [4].

Differential Diagnosis

Confronting a patient with proctitis is challenging as the differential diagnosis is broad; however, a systematic approach considering symptoms and etiologic factors will help narrowing the diagnosis. In Table 8.1, we classified the potential etiologies in four main categories: infectious proctitis, infectious proctocolitis, autoimmune, and others. Those with the most common etiology, as indicated by an asterisk, will be discussed in more detail.

Table 8.1 Potential etiologies of proctitis

Infectious proctitis	Infectious proctocolitis	Autoimmune	Others
∗*Neisseria gonorrhoeae* ∗*Chlamydia trachomatis* (serovars D through K) ∗Lymphogranuloma venereum ∗Syphilis ∗Herpes simplex virus ∗Human papillomavirus ∗Human immunodeficiency virus Cytomegalovirus *Mycobacterium tuberculosis* Ulceration (rare) *Haemophilus ducreyi* (chancroid) *Klebsiella granulomatis* (granuloma inguinale) *Mycoplasma genitalium* Granuloma inguinale	∗*Giardia lamblia* *Shigella* species *M. avium-intracellulare* *Campylobacter* species *Salmonella* species *Entamoeba histolytica* *Yersinia enterocolitica* *Clostridium difficile*	∗Crohn's disease ∗Ulcerative colitis Lymphoid follicular proctitis Behçet's syndrome Lymphoma ischemia Amyloidosis	Hemorrhoids Irritable bowel syndrome ∗Anal fissures Trauma Foreign bodies Chemical proctitis

∗Star indicates more common etiology

Infectious Proctocolitis

Inflammatory Bowel Disease (IBD)

The most common symptoms of proctitis of any etiology are lower abdominal pain, diarrhea, rectal bleeding, and tenesmus [3]. One of the most frequent causes of proctitis in the general population is IBD, which includes *Crohn's disease* (CD) and *ulcerative colitis* (UC) [2]. They are characterized by abdominal pain, bloody diarrhea, and weight loss [5]. Often these conditions are diagnosed in adolescence and young adulthood, with a peak in the second and third decade of life [5, 6]. The cause of IBD is largely idiopathic but involves an abnormal intestinal immune response in a person who is genetically predisposed [2, 5]. About 30% of patients with UC develop "ulcerative proctitis," which involves inflammation only of the rectum [2].

Infectious Proctitis

The most common causes of infectious proctitis include STIs, which result from the direct inoculation of the rectum with the disease pathogen in question [7]. Despite the frequency of IBD, the incidence of infectious proctitis such as those caused by *Neisseria gonorrhoeae* (NG), *Chlamydia trachomatis* (CT), lymphogranuloma venereum (LGV), syphilis, herpes simplex virus (HSV), human papillomavirus (HPV), or human immunodeficiency virus (HIV) has significantly increased over the last two decades, especially among men who have sex with men (MSM) [2, 8, 9]. Sexually transmitted proctitis often presents with tenesmus, rectal discharge, rectal bleeding, rectal pain, and constipation [1, 4, 7]; however, the differentiation in etiology is often indistinguishable from IBD without further history taking and diagnostic evaluation [1].

Chlamydia trachomatis

In the USA, the most commonly reported STI is CT with an estimated annual incidence of 2.86 million infections annually [10]. CT is most prevalent among those less than 24 years of age, and rectal CT is most common among men who have sex with men (MSM) [2, 7, 10, 11]. There are 18 known serovars, with B and D through K being responsible for CT urethritis, cervicitis, and proctitis [5, 7, 10]. Chlamydia is asymptomatic in up to 70% of cases; however, patients may present with tenesmus, rectal pain, fever, pruritus, diarrhea, or anal discharge [1–3, 7]. Proctoscopy findings, if present, often reveal nonspecific inflammation, erythema, deep ulcers, and granulomas with mucopurulent exudates [1, 7, 12]. Lymphoplasmacytic infiltrates, cryptitis, crypt abscess, and granulomas may be observed on histological exam [12]. Both the proctoscopy and histology findings of CT may also be typical findings in IBD [12].

LGV is a sexually transmitted infection caused by *Chlamydia trachomatis* serovars L1-L3 [1, 7, 10, 11, 13]. Within days to weeks after exposure, an ulcer or papule may appear at the site of inoculation and self-resolve before the person presents for medical treatment [2, 11, 13]. Most commonly, an initial LGV infection presents with unilateral inguinal and/or femoral lymphadenopathy as well as tenesmus, rectal bleeding, lower abdominal cramping, mucoid rectal discharge, constipation, and/or rectal pain [1, 7, 10, 11, 13]. Among MSM, a significant predictor of LGV has been shown to be the presence of tenesmus alone or in combination with constipation [14]. If left untreated, LGV may progress to include bilateral or unilateral fluctuant buboes and/or anorectal ulcers along with associated fevers, arthralgias, myalgias, malaise, and weight loss [1, 2, 11, 13, 15]. In the most severe cases, a person may develop systemic symptoms such as abscesses, fistulas, genital elephantiasis, stricture formation, and sterility [3, 4, 11, 15]. In these advanced cases, proctoscopy may reveal pronounced inflammation, ulceration, friable mucosa, mucopurulent discharge, and strictures [1, 7, 12, 13, 16]. Given the strong resemblance to IBD, LGV may be distinguished based on the presence of mucopurulent discharge and painful lymphadenopathy [3, 13, 16]. LGV was previously thought to be relatively uncommon; however, over the last decade, a number of outbreaks have been documented among MSM in Europe and North America, and the incidence of infection is on the rise [2–4].

Neisseria gonorrhoeae

Neisseria gonorrhoeae is a gram-negative, oxidase-positive diplococcus [17]. NG infection is the second most common STI in the USA, and similar to CT, up to 50% of males and 95% of females with rectal gonorrhea may present asymptomatically [7]. Symptoms, if present, often occur about 5 days after transmission and may include rectal discharge, tenesmus, pruritus, bleeding, or constipation [1, 2, 4, 7]. Rectal gonorrhea most often results from receptive anal intercourse but can also result from the transmucosal spread of genital fluid in women [3]. Proctoscopy may be normal or have nonspecific findings such as mucosal erythema, edema, and a purulent discharge [16]. NG infection also has the ability to disseminate and can result in polyarthralgia, septic arthritis, tenosynovitis, or petechial or pustular lesions on peripheral body parts [11].

Syphilis

Syphilis is caused by the spirochete *Treponema pallidum*, and inoculation occurs via contact with the mucocutaneous syphilitic lesions [7]. While overall rates of syphilis are low compared to chlamydia or gonorrhea, they have increased significantly in the past few years with over 90% of cases occurring among MSM, particularly HIV+ MSM [7, 8]. The main symptom of primary syphilis is a painless chancre at the site of infection [2, 3]. When transmission occurs in the rectum, the chancre may actually be tender; however, it often goes unnoticed or is mistaken for an anal

fissure [1]. Primary symptoms may also include rectal discharge, urgency, tenesmus, or the presence of multiple chancres [2, 4, 7]. During secondary syphilis, a maculopapular rash appears on the hands and feet, and systemic symptoms such as proctitis, fever, malaise, arthralgias, sore throat, headache, and weight loss may occur [1, 2, 7]. Syphilitic proctitis may present with ulcerations or mass lesions that would be found to contain *Treponema pallidum* on biopsy and occurs with or without the pathognomonic clinical symptoms of syphilis [18]. On endoscopy, the most common findings are ulcerations [19]. Condyloma lata are verrucous-looking, plaque-like lesions on the genitals that may occur during this phase. They are highly infectious and often confused with HPV [3, 20]. Tertiary syphilis can occur several years after initial infection and can cause major systemic neurological and cardiovascular disease. In the GI tract and buttocks, granulomatous nodules or ulcerations called gummas may occur leading to worsening proctitis [3].

Herpes Simplex Virus

Herpes simplex virus causes vesicular eruptions near mucocutaneous junctions which then ulcerate and spontaneously resolve over several days [1]. There are two types: HSV-1, which typically causes lesions around the mouth, and HSV-2, which typically causes genital lesions. About 20% of the general population has been infected with HSV-2; however, due to the frequency of oral-genital contact, HSV-1 and HSV-2 may be found in each location [7]. HSV reactivation may occur following the initial HSV infection, because HSV ascends into the peripheral sensory nervous system and then lies dormant in the sensory of autonomic ganglia [3]. Reactivation occurs in 60% of HSV-1 and 90% of HSV-2 infections [3]. HSV proctitis results from the spread of the infection from the perianal skin, into the anal canal and rectum. HSV proctitis most often occurs among those who are immunocompromised or those who have anoreceptive sex [7]. Symptoms may include rectal pain, rectal discharge, tenesmus, and rectal bleeding [2, 4]. During the acute phase of HSV proctitis, symptoms may be severe and can include difficulty urinating, sacral paresthesias, and temporary fecal incontinence [4, 7, 10]. In extensive cases, there may be perianal erythema and/or ulcerations that can be confused with *Candida* infections. Patients will often report extreme pain on digital rectal examination and anoscopy. Sigmoidoscopy often reveals mucosal edema and ulcerations [4, 7].

Giardia lamblia

Giardia lamblia is a protozoon that is spread by the fecal oral route and can thus be spread through sexual transmission. Most commonly sexual transmission occurs among MSM [3]. The protozoa attach and proliferate on the brush border of the duodenum and the jejunum [3]. Symptoms include foul-smelling steatorrhea, diarrhea, and abdominal pain and cramping [3, 11]. Symptoms often occur about 2–3 weeks after infection, and in the most severe cases, proctitis is apparent [3].

HPV

Human papillomavirus will be contracted by most sexually active adults at some point in their lifetime [11]. There are over 100 types of HPV, and over 40 are known to infect the genital region [10, 11]. Most HPV infections are asymptomatic and resolve spontaneously; however, some types of HPV can cause cancers of the vagina, penis, and rectum, and others can cause genital warts [11]. About 95% of anal cancers are linked to HPV, specifically types 16 and 18 [10, 11]. Genital warts caused by HPV are also known as condyloma acuminata (multiple warts) or condyloma acuminatum (a singular wart). Genital warts are caused by HPV types 6 or 11 in 90% of cases [10]. Symptoms of HPV-related cancer and genital warts can both present similar to proctitis. Symptoms of genital warts include palpable lesions, bleeding, pain, or pruritus, and the exam often reveals external lesions that are fleshy and cauliflower in nature (Fig. 8.1). These lesions may be singular or

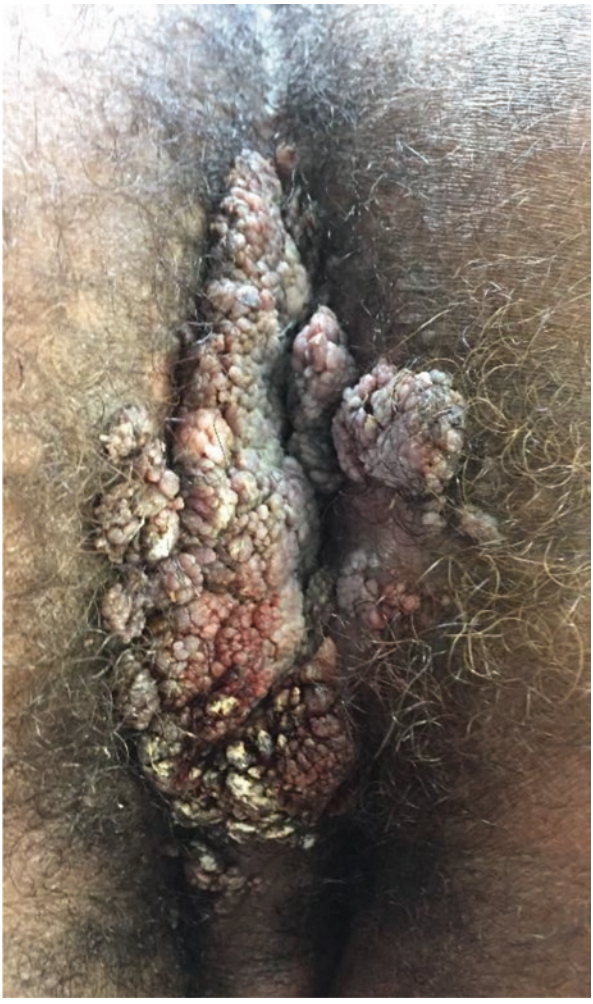

Fig. 8.1 Anal warts in an MSM young adult who is HIV+

extensive, covering the entire anogenital region. Genital warts can also occur within the anal canal, most commonly distal to the dentate line, and may or may not be palpable on digital rectal exam [10].

Anal Fissures

The term anal fissure describes a tear in the epithelial lining of the anal canal that may result most commonly from constipation or anal trauma. Symptoms of anal fissures often resemble symptoms of proctitis as patients often report hematochezia, rectal pain, or spasms that can last for several hours following a bowel movement. Most will resolve spontaneously; however, chronic fissures are those that last longer than 4–6 weeks. Chronic anal fissures may have exposed anal sphincter muscle, a sentinel tag, or hypertrophied anal papilla. Anal fissures may or may not be visible on exam [21].

Diagnosis

IBD

Diagnosis of IBD is often not straightforward given the lack of highly sensitive serologic testing and often involves an array of serologic, stool, and endoscopic findings [5]. Frequently abnormal laboratory findings in patients with IBD include anemia, thrombocytosis, elevated inflammatory markers, and/or hypoalbuminemia [5]. There is a commercially available IBD diagnostic panel that includes serologic and genetic markers; however, it has a relatively low sensitivity (65–75%) [5]. Examination of stool may reveal fecal calprotectin, which is emerging as a highly sensitive (98%) indicator of IBD in patients with intestinal inflammation [5]. Ultimately, patients suspected of IBD will need to undergo esophagogastroduodenoscopy and ileocolonoscopy with biopsy in order to diagnose IBD. A CT scan or MRI may be useful for assessment of the IBD, but is not diagnostic and should not be used in place of endoscopic evaluation [5].

Gonorrhea

Microscopic examination and gram stain of rectal exudate may be helpful in the initial evaluation of a symptomatic patient, but given their low sensitivity are not considered sufficient testing methods alone or in tandem. However, the presence of gram-negative diplococci in a symptomatic patient can be considered diagnostic of NG. Cultures should be placed in selective media when coming from non-sterile

sites, and inoculation should happen as soon as possible as the organism is labile in the environment [11]. Nucleic acid amplification testing (NAAT) is available for detection of NG and has become the preferred method of testing. While NAAT testing is more sensitive than culture, it is not FDA-cleared in rectal, oropharyngeal, or conjunctival samples [3, 4, 11]. To mitigate this, some laboratories have validated and achieved Clinical Laboratory Improvement Amendments (CLIA) regulatory requirements for NAAT testing in rectal and oropharyngeal samples [7, 11].

Chlamydia and LGV

Similar to diagnostic evaluation of NG, the NAAT is the recommended diagnostic test of choice for the detection of rectal as well as urethral and oropharyngeal CT [3, 7, 11]. This testing is also not FDA-cleared, but like GC, many laboratories have undergone CLIA approval for testing of these specimens [11].

Diagnostic testing of LGV is limited, and thus diagnosis and empiric treatment should be given based on clinical findings, epidemiological data, and the exclusion of other etiologies [4, 7, 11]. Patients presenting with symptoms of proctitis should be tested with a NAAT for CT in order to support a clinical diagnosis of LGV when CT is detected [3, 11]. In order to distinguish between LGV and non-LGV CT serovars, PCR-based genotyping must be performed; however, this testing is currently not widely available, and the results of such testing are not garnered in a timeframe that would affect clinical decision-making [3, 4, 7, 11]. Chlamydia serology may be available and provide some support for a diagnosis of LGV; however, the interpretation of these results has not been standardized nor their use validated in the setting of a patient presenting with proctitis [11].

Syphilis

Darkfield examination and tests to detect *T. pallidum* in lesion exudates or tissue samples are considered definitive methods of diagnosis [3, 7, 11]. However, currently there are no commercially available tests to detect *T. pallidum*, although some laboratories provide locally validated tests to detect the presence of *T. pallidum* DNA [11]. A presumptive diagnosis of syphilis can be made using a combination of two tests, a nontreponemal and a treponemal test. Examples of nontreponemal tests include the venereal disease research laboratory (VDRL) and rapid plasma reagin (RPR), and examples of treponemal tests include fluorescent treponemal antibody-absorbed (FTA-ABS) test, the *T. pallidum* passive particle agglutination [TP-PA] assay, several enzyme immunoassays such as the *T. pallidum* enzyme immunoassay (TP-EIA), the *T. pallidum* chemiluminescence immunoassay (TP-CIA), immunoblots, and rapid treponemal assays [3, 7, 11]. *T. pallidum* antibodies may take up to 12 weeks to be detected in the serum [3]. Traditional testing algorithms involve

testing first with the nontreponemal test followed by a confirmatory treponemal test [11, 22]. Since this testing algorithm misses a small percentage of patients with a negative nontreponemal test, but a positive treponemal test, some laboratories have reversed the order of the traditional testing algorithm [11, 22]. In the reversed sequence of syphilis testing, if there is a positive treponemal test followed by a negative nontreponemal test, then an alternative treponemal test should be performed. If the second treponemal test is negative and clinical suspicion is low, no follow-up is needed; however, if it is positive and there is no history of syphilis infection and treatment, then the person should be treated for late latent syphilis (if the person was previously treated and there are no signs of reinfection then no further treatment is required) [22]. The importance of the additional positive test results identified with the reversed algorithm testing is unclear as there are no established follow-up testing algorithms and it may result in overdiagnosis and treatment [11, 22]. In addition to supporting a diagnosis, nontreponemal tests such as the VDRL and RPR are monitored to assess response to therapy. A fourfold decrease in titers (e.g., 1:32 to 1:8) over the course of 6 months to a year is considered diagnostic for a therapeutic response to syphilis treatment, while a fourfold increase in titers (e.g., from 1:16 to 1:64) is considered a reinfection [11]. Most patients will maintain a positive treponemal test indefinitely, while about 15–25% will revert back to a seronegative state within 2–3 years of treatment [11].

HSV

Given the increased sensitivity, nucleic acid amplification testing (HSV DNA PCR) has replaced culture and Tzanck smears as the recommended HSV test of choice. PCR assays can be performed on rectal biopsy or exudate specimens [2, 3, 11]. Histopathology may also be performed on mucosal biopsies to confirm an HSV diagnosis; however, results are less sensitive [2]. The absence of HSV on PCR does not necessarily rule out infection with HSV, especially if the patient has no active lesions [11]. Serologic testing, which distinguishes HSV-1 from HSV-2 infection, may be appropriate in certain settings, but should not be used as a routine screening tool in the asymptomatic general population. Scenarios when serologic testing may be useful include the evaluation of a patient with HSV symptoms but a negative HSV PCR, laboratory confirmation of an HSV diagnosis in a patient who was diagnosed clinically, or testing of a patient who reports an HSV infection in their partner. HSV evaluation should be considered, even if the patient does not report complaints of active lesions as HSV proctitis may present without external rectal lesions [23].

Giardia lamblia

The three most widely available techniques for diagnosing *Giardia lamblia* are direct microscopy of feces to reveal trophozoites or oocysts, rapid enzyme immunoassay testing, and real-time PCR with fluorescent detection probes [24]. Direct microscopy

remains the most frequently performed testing for *Giardia lamblia*; however, due to intermittent shedding of the *Giardia lamblia* cyst, microscopy of only one stool sample has been shown to have low sensitivity [24]. It is thus recommended to evaluate three stool samples collected over a period of several days to increase sensitivity [3, 24]. Both rapid immunoassay and PCR testing have shown to be effective with higher sensitivity than microscopy of a single stool specimen. Unfortunately, these newer testing modalities remain less specific than microscopy. Direct microscopy of multiple samples by a trained microscopist is generally considered the test of choice for *Giardia lamblia*. However, when multiple samples cannot be obtained, a serologic test should also be ordered to improve the accuracy of the results [24].

HPV

The diagnosis of anal warts and thus the diagnosis of HPV are generally made based on visual inspection. Confirmation of genital warts may be made on biopsy; however, specific HPV testing is not recommended for the diagnosis of genital warts [11]. Additionally, we know that HPV is a major cause of anal carcinoma among MSM, especially HIV+ MSM. Clear guidelines have not been established for the screening of anal carcinoma; however, it is generally recommended that MSM receive a screening anal Pap smear to detect atypical cellular morphology and HIV+ MSM should be screened with anal Pap smears annually [8]. Any atypia found in the Pap smear (atypical squamous cell of undetermined significance (ASC-US), low-grade squamous intraepithelial lesion (LSIL), high-grade squamous intraepithelial lesion (HSIL), or cancer) should then be followed up with high-resolution anoscopy in order to classify the atypia as either low-grade or high-grade dysplasia [8, 25].

Anal Fissures

The diagnosis of anal fissures is made clinically based on symptoms and physical exam. Upon examination, a linear separation of the anoderm may be visualized. This may be visible on simple office examination but may also require anoscopy for identification [21].

Treatment

IBD

IBD is not curable, so the goal of treatment using a variety of treatment modalities is to induce and maintain remission in order to improve the quality of life of the patient and eliminate complications. Corticosteroids remain an effective therapy in

inducing remission, but about half of all patients will become dependent on them or require surgical management. In flares of CD, exclusive enteral nutrition for 8–12 weeks is a therapy found to have similarly effective rates of inducing remission as corticosteroids [5]. Aminosalicylates such as mesalamine have an anti-inflammatory effect and have shown to have good outcomes at inducing and maintaining remission of IBD, particularly among those with UC [2, 5]. Immunomodulators such as methotrexate and thiopurine drugs have been used for the last 30 years in the maintenance of remission given their delayed onset of action. Perhaps the most revolutionary therapy for IBD is anti-TNF biologics, as they have been shown to be highly successful at inducing remission as well as promoting healing of the intestinal mucosa. Among those patients with refractory IBD, especially those with CD, surgical resection of the diseased colon is often a highly effective therapeutic option [5]. Fecal microbiota transplantation (FMT) has emerged as a possible treatment for Crohn's and UC. The limited data that exists has found that FMT offers equivocal benefit; however, there are currently at least 20 clinical studies examining FMT as a therapeutic treatment option for IBD. Until more robust data has been collected to indicate significant improvements in IBD patients treated with FMT, FMT should continue to be considered an experimental treatment option [26].

Gonorrhea

Empiric treatment of GC is recommended for anyone that presents with a high index of suspicion for infection [4]. Due to the increasing rates of antimicrobial-resistant GC, the only CDC-recommended first-line therapy for the treatment of GC is ceftriaxone 250 mg IM and azithromycin 1000 mg oral, which covers for both GC and CT [2, 7, 11]. If ceftriaxone is not available, cefixime 400 mg orally in a single dose plus azithromycin 1 g orally in a single dose may be administered. Important to note is that only 2.5% of patients who report a history of reactions to penicillin will have a reaction to a first-generation cephalosporin and even fewer will have a reaction to a third-generation cephalosporin such as ceftriaxone [11]. If a patient reports a severe penicillin allergy (anaphylaxis, Stevens-Johnson syndrome, or toxic epidermal necrolysis), ceftriaxone should be avoided. If resistant GC is suspected, patients should be retreated with ceftriaxone and azithromycin (most likely to be reinfection), and antibiotic susceptibilities to *N. gonorrhea* should be ordered if the organism is grown. Possible alternative treatment regimens include a single dose of oral gemifloxacin 320 mg plus oral azithromycin 2 g or treatment with a single dose of gentamicin 240 mg IM plus azithromycin 2 g orally [11]. If disease disseminates, treatment should occur under the consultation of an infectious disease specialist and would likely require hospitalization and utilization of intravenous ceftriaxone in addition to azithromycin [11].

Chlamydia/LGV

As in the recommendations of empiric treatment for GC, empiric treatment of CT is also recommended in a patient with suspected CT. First-line treatment of chlamydia includes azithromycin 1 g orally or doxycycline 100 mg twice a day for 7 days [3, 11]. Data shows that treatment efficacy for 1 g of azithromycin is between 83.6% and 85%. Higher rates of reinfection and treatment failures were associated with higher CT organism load. The use of doxycycline as first-line therapy is recommended in Europe and Australia; however, to date there are no randomized control trials comparing the efficacy of azithromycin and doxycycline in the treatment of rectal chlamydia [27].

Treatment for LGV is also begun empirically with doxycycline 100 mg twice daily for 21 days as first-line therapy [2, 11, 13].

Syphilis

Treatment of syphilis is dependent on the stage of syphilis. Treatment of primary and early latent syphilis involves a single dose of 2.4 million units of benzathine penicillin G parenterally [3, 7]. Late latent syphilis or latent syphilis of unknown duration or tertiary syphilis without neurological signs involves three doses of 2.4 million units of benzathine penicillin G parenterally administered at 1-week intervals. In a patient with a documented penicillin allergy, second-line treatment is doxycycline 100 mg twice a day for 14 days or tetracycline 500 mg four times a day for 14 days [11]. Quantitative nontreponemal serologic testing should be offered at a minimum of 6-, 12-, and 24-month intervals in order to monitor for a fourfold decrease in titer within 12–24 months of therapy [2, 7, 11].

HSV

Treatment of genital HSV varies depending upon whether or not the patient has a prior history of genital HSV episodes. Despite the fact that HSV outbreaks will spontaneously resolve, all patients presenting with an initial episode of HSV should be treated with HSV antivirals due to the increased risk of severe or prolonged symptoms. Treatment options include acyclovir 400 mg orally three times a day for 7–10 days, acyclovir 200 mg orally five times a day for 7–10 days, valacyclovir 1 g orally twice a day for 7–10 days, or famciclovir 250 mg orally three times a day for 7–10 days [11]. While treatment will resolve symptoms, once infected with HSV, the virus will remain within the body for life [11]. Nearly all patients who experience an initial outbreak will experience at least one recurrent episode of

HSV. Treatment of each episode reduces the severity and duration of symptoms. Acceptable first-line treatment recommendations include acyclovir 400 mg orally three times a day for 5 days, acyclovir 800 mg orally twice a day for 5 days, acyclovir 800 mg orally three times a day for 2 days, valacyclovir 500 mg orally twice a day for 3 days, valacyclovir 1 g orally once a day for 5 days, famciclovir 125 mg orally twice daily for 5 days, famciclovir 1 gram orally twice daily for 1 day, and famciclovir 500 mg once, followed by 250 mg twice daily for 2 days [11]. For those patients with frequent HSV recurrences, suppressive daily therapy with antivirals should be considered. It is important to note that while a person may be asymptomatic, they continue to have viral shedding, which puts sexual partners at risk of infection [2, 7, 11]. Patients may also be offered symptomatic relief of lesions by using oral analgesics and sitz baths [2, 7].

Giardia lamblia

Once diagnosis of *Giardia lamblia* has been confirmed, recommended treatments include tinidazole 2 g for one dose, nitazoxanide 500 mg twice a day for 3 days, or metronidazole 250 mg three times a day for 5–7 days (is the least expensive but is also the one with the highest frequency of gastrointestinal side effects) [3].

HPV

Anogenital warts may resolve spontaneously within 1 year. If symptoms are severe and do not resolve or the patient requests treatment, then several treatment modalities exist. In order to determine the best treatment for the patient, the size, number, and location of warts should be considered as well as cost, side effects, and convenience of treatment in conjunction with the patient preference. Treatments that the patient can apply at home include imiquimod 3.75% or 5% cream, podofilox 0.5% solution or gel, or sinecatechins 15% ointment. Provider-administered treatment includes cryotherapy with liquid nitrogen or cryoprobe; surgical removal by either tangential scissor excision, tangential shave excision, curettage, laser, or electrosurgery; or trichloroacetic acid (TCA) or bichloroacetic acid (BCA) 80–90% solution [11].

Anal dysplasia caused by HPV is classified as low-grade or high-grade dysplasia and treated accordingly. Low-grade dysplasia is not classified as pre-cancerous and does not require treatment except at the discretion of the clinician. There is currently no preferred treatment of high-grade dysplasia, and thus it depends on the location of the dysplasia and provider preference. When the dysplasia is located within the anal canal, treatment often involves surgical intervention using high-resolution anoscopy with targeted ablation, laser, or electrocautery. If the high-grade dysplasia is outside of the anal canal, topical treatments such as imiquimod or 5-fluorouracil may be applied. Alternatively, trichloroacetic acid (TCA) at varying concentrations between 35% and 80%, infrared coagulation (IRC), and photodynamic therapy may be considered [25].

Anal Fissures

Anal fissures typically resolve spontaneously and do not require intervention. Chronic anal fissures are those lasting more than 4–6 weeks and may require medical management. First-line therapy includes managing constipation, using bulking agents, and topical nitroglycerin or calcium channel blockers. In difficult-to-treat cases, topical botulinum toxin and lateral internal sphincterotomy may be considered [21] (Table 8.2).

Table 8.2 Proctitis: common causes, clinical manifestations, and treatment

Organism	Common manifestations	Treatment
Inflammatory bowel disease	Abdominal pain, bloody diarrhea, weight loss	Corticosteroids, exclusive enteral nutrition, aminosalicylates, immunomodulators, anti-TNF biologics, surgical resection
Neisseria gonorrhoeae	Often asymptomatic. Symptoms if present may include rectal discharge, tenesmus, pruritus, bleeding, or constipation	Ceftriaxone 250 mg IM and azithromycin 1000 mg oral
Chlamydia trachomatis	Often asymptomatic. Symptoms if present include tenesmus, rectal pain, fever, pruritus, diarrhea, or anal discharge	Azithromycin 1000 mg oral
Lymphogranuloma venereum	Unilateral inguinal and/or femoral lymphadenopathy, tenesmus, rectal bleeding, lower abdominal cramping, mucoid rectal discharge, constipation, and/or rectal pain	Doxycycline 100 mg BID for 21 days
Syphilis	Primary symptoms: painless chancre but otherwise may be asymptomatic. Rectal discharge, urgency, tenesmus Secondary syphilis: maculopapular rash on the hands and feet and systemic symptoms such as proctitis, fever, malaise, arthralgias, sore throat, headache, and weight loss	Primary and early latent syphilis: single dose of 2.4 million units of benzathine penicillin G parenterally Late latent syphilis or latent syphilis of unknown duration: three doses of 2.4 million units of benzathine penicillin G parenterally administered at 1-week intervals for 3 weeks

(continued)

Table 8.2 (continued)

Organism	Common manifestations	Treatment
HSV	Vesicular eruptions near mucocutaneous junctions which then ulcerate and spontaneously resolve over several days	Initial outbreak: Acyclovir 400 mg orally three times a day for 7–10 days, acyclovir 200 mg orally five times a day for 7–10 days, valacyclovir 1 g orally twice a day for 7–10 days, or famciclovir 250 mg orally three times a day for 7–10 days Recurrent outbreaks: Acyclovir 400 mg orally three times a day for 5 days, acyclovir 800 mg orally twice a day for 5 days, acyclovir 800 mg orally three times a day for 2 days, valacyclovir 500 mg orally twice a day for 3 days, valacyclovir 1 g orally once a day for 5 days
Giardia lamblia	Foul-smelling steatorrhea, diarrhea, and abdominal pain and cramping	Tinidazole 2 grams ×1 Nitazoxanide 500 mg twice a day for 3 days Metronidazole 250 mg three times a day for 5–7 days [3]
HPV	Often asymptomatic. If warts are present, palpable fleshy lesions, rectal bleeding, or pruritus may occur	Anal warts: Self-administered creams: imiquimod 3.75% or 5% cream, podofilox 0.5% solution or gel, or sinecatechins 15% ointment. Cryotherapy with liquid nitrogen or cryoprobe, surgical removal, TCA or BCA 80–90% solution [11] Anal dysplasia: Low-grade anal dysplasia – generally does not require treatment High-grade dysplasia – surgical intervention, imiquimod or 5-fluorouracil, TCA at varying concentrations between 35 and 80%, infrared coagulation, or photodynamic therapy
Anal fissures	Bright red blood during bowel movements, rectal pain, or spasms	Anal fissures typically resolve spontaneously. Chronic anal fissures: manage constipation, bulking agents, topical nitroglycerin or calcium channel blockers, topical botulinum toxin, and lateral internal sphincterotomy

Prevention

The primary method of preventing proctitis due to STIs involves consistently demonstrating safe sex practices. Examples of safe sex practices include, but are not limited to, using condoms for every sexual act, reducing the number of sexual partners, limiting sexual intercourse to one mutually monogamous partner with whom you know to be uninfected with any STIs, or abstaining from sex [4, 10]. Frequent testing and subsequent treatment, if necessary, for STIs and HIV as well as offering partner treatment is one way to reduce the severity of symptoms and decrease the spread of STIs causing proctitis. It is also important when testing for STIs to complete comprehensive testing for all STIs at all anatomic sites used during sexual acts

in order to identify, treat, and stop the spread of infection [2]. All of those infected with an STI should also be educated to remain abstinent for at least 7 days after receiving (or their partner receiving) treatment in order to reduce the risk of reinfection [10]. An inflamed rectum has been shown to increase the risk of HIV transmission by up to ninefold, further underlying the need for timely evaluation and treatment of the proctitis patient [2]. Prevention of HPV disease with the administration of the bivalent or quadrivalent HPV vaccine is highly encouraged and is recommended to be given starting between 11 and 12 years of age in boys and girls through 21 years of age. Additionally, women and high-risk men who are unvaccinated or have not finished the three-dose series should receive vaccination through 26 years of age [11].

Other Considerations (Specialty Populations)

HIV-/AIDs-Related Proctocolitis

HIV commonly affects the gastrointestinal tract in various ways throughout the course of the disease and has been shown to cause nonspecific proctitis and colitis [7, 28]. Studies have shown that during acute HIV, the virus is found to target and deplete the CD4+ memory T cells in the gut. Through this mechanism, the gut experiences early replication of the virus and is a target for immunosuppression. One study found that among 20 MSMs who were acutely infected with HIV, 10% were diagnosed with proctitis on endoscopy [28].

Among those living with HIV, there is also a high rate of anal lesions. One study revealed that among a random sample of patients infected with HIV, 44% had at least one anal macroscopic lesion, about 23% had HPV-related lesions, 14% had hemorrhoids, and 11% had anal fissures [29]. Syphilis and HSV have been found to be two of the most common causes of anogenital lesions [30]. Additionally, both HIV and syphilis have been demonstrated to be risk factors for LGV, further increasing the risk of proctitis in those infected with HIV [2, 31]. Additional studies among MSM presenting with proctitis have shown that those with HIV have higher rates of HSV, LGV, and proctitis caused by two or more infectious etiologies [23].

Case Conclusions

The patient is given empiric treatment for chlamydia and gonorrhea in accordance with CDC guidelines based on his mucoid rectal discharge and history of unprotected anal sex. Prior to receiving this treatment however, a variety of diagnostic STD testing including NAAT GC/CT testing from a rectal swab, throat swab, and urine sample as well as RPR and HIV blood testing were ordered. His provider also

wrote a prescription for topical Imiquimod to treat the anal condyloma seen on physical exam and started the HPV vaccination series. The provider then counseled the patient on safe sex practices including the consistent use of condoms and abstaining from sex for at least 7 days from the time both the patient and their partners were treated to ensure adequate treatment and prevent reinfection. One to 2 days later, results revealed a positive rectal gonorrhea and chlamydia NAAT result as well as a positive chlamydia throat swab. All other STD test results were negative. Upon calling the patient with his test results, the provider encouraged the patient to disclose the results of his testing with his sexual partners and encourage them to get treatment.

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Chapter 9
Pharyngitis

Emily Popler and Judson J. Miller

Case Study
A 22-year-old college student visited his student health clinic with a chief complaint of sore throat and feeling "under the weather." He had no major medical problems but reported a past history of having had "tonsillitis several times a year," which typically resolves on its own without treatment. He also reported that he had similar but more severe symptoms several weeks ago. At that time, he had significant throat pain and could see pus on his tonsils. He does not believe that he had a fever at that time. He does note that the more severe sore throat that he had several weeks ago developed several days after he "hooked up with someone he met at a bar." On further questioning, it was determined that 1 week prior, the student had engaged in oral sex with a new partner. His partner developed genital discharge and was subsequently diagnosed with gonorrhea.

Questions for Consideration
- What additional history do you need to obtain from the patient?
- What are you looking for on your physical exam?
- What tests, if any, should be performed?
- How should you counsel the patient?

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Introduction

Pharyngitis is defined as an inflammation of the pharynx and mucous membranes, with multiple subtypes including atrophic, gangrenous, membranous, ulcerative, and ulceromembranous [1]. Adolescent and young adult patients are more likely to describe pharyngitis simply as a "sore throat." However, using this colloquial definition complicates the picture somewhat – since an adolescent patient presenting with a complaint of "sore throat" may be using the term to refer to a variety of painful or irritating symptoms occurring in the oral cavity, pharynx, larynx, or neck tissue [2]. The term "sore throat" may reference a much broader set of symptoms and anatomy. Thus, in discussing pharyngitis caused by sexually transmitted infections (STIs), this chapter will also mention STIs that most commonly manifest in the oral cavity or along the oropharyngeal space.

Differential Diagnosis

The differential diagnosis for an adolescent presenting with the complaint of sore throat is broad and includes infectious causes, allergic causes, irritants, and trauma [2]. In recent years, pharyngitis has been identified as one of the top five diagnoses associated with ambulatory clinic visits for all pediatric-aged patients [3]. Among pediatric patients in the United States, common infectious etiologies of pharyngitis include a variety of bacterial and viral causes, including group A beta-hemolytic streptococcus, Epstein–Barr virus, cytomegalovirus, adenovirus, Coxsackie virus, and influenza. In sexually active adolescents, it is also important to consider viral and bacterial STIs as a possible cause of oropharyngeal symptoms. Gonorrhea, chlamydia, herpes simplex virus (HSV), syphilis, and human papilloma virus (HPV) may be present in the oropharyngeal area and may present with symptomatic pharyngitis. Adolescents with acute human immunodeficiency virus (HIV) infection may also present with pharyngitis as part of a broader syndrome. At the same time, it is important to note oropharyngeal STIs are frequently asymptomatic. Thus, this chapter will also include a discussion of the major sexually transmitted pathogens that may be present in the oropharyngeal space even when patients have no complaint of "sore throat."

Oral Sex Attitudes and Practices of Adolescents

"Oral sex" is a general term that encompasses multiple types of sexual activity. Most frequently, it is used to refer to orogenital sexual activity during which the mouth, tongue, teeth, and pharynx of an individual may come in contact with the genital area of their partner(s). However, the term also includes oroanal sexual

activity during which the mouth, tongue, or teeth are used to stimulate the anal or rectal area of an individual's sexual partner(s) [4]. STIs may be passed from the genitals to the oral cavity and pharynx and some can be passed from the oropharyngeal area to the genitals. This transmission usually occurs in the exchange of body fluids such as semen, vaginal secretions, blood, saliva, fecal material, or through contact of a skin lesion or sore [5, 6].

There is a considerable body of research, including surveillance data, focused on adolescent sexual behavior. However, most of this research focuses on vaginal, or sometimes anal, intercourse – investigation regarding oral sex practices of adolescents has lagged behind considerably. For example, the Center for Disease Control's (CDC) Youth Risk Behavior Surveillance System (YRBSS) [7] tracks adolescent behaviors in six major areas that contribute to adolescent morbidity and mortality. The YRBSS includes questions about sexual behavior, asks survey participants about their sexual identities, and specifies the sex of their partners [8]. However, although this is a major national account of adolescent sexual behavior, no data on oral sex is collected. Should we assume that the lack of information about oral sex reflects that only a small subset of adolescents is actually engaging in oral sexual activity? In fact, the opposite is true.

The CDC's National Health Center for Health Statistics does collect some information about oral sex through the National Survey of Family Growth (NSFG) [9]. For adolescents aged 15–19 years old, information regarding oral sexual activity is asked about specifically, although notably only pertaining to oral sex occurring with opposite-sex sexual partners. In this group, from 2011 to 2013, 51.2% of young men and 47.4% of young women reported ever engaging in oral sex. Available reports on oral sex from the NSFG are not disaggregated by age, so that data for adolescents having oral sex with same sex partners is combined with data from older adults with a total range of 15–44 years old. Within that group, 5.5% of all males reported oral sex with another male [9, 10]. Further, 17.4% of all women reported sexual activity with another woman, presumably including oral sex (but not specified in the published reports) [9, 10]. The Henry J Kaiser Family Foundation's *National Survey of Adolescents and Young Adults: Sexual Health, Knowledge, Attitudes and Experiences* is administered to approximately 1800 youth and concludes that about one-third of adolescents surveyed ages 15–34 have had oral sex. Furthermore, three-quarters of those individuals who reported that they have had sexual intercourse also reported having oral sex [11].

Many assumptions also exist about the oral sex practices of adolescents. The current available research shows that some of these theories are more accurate than others. Let us examine three of these common beliefs:

1. Adolescents often engage in oral sex as a way of delaying engaging in sexual intercourse.

   (a) Kaiser's National Survey of Adolescents and Young Adults [11] did find that about one-quarter of sexually active adolescents stated that they had used oral sex as a way of delaying sexual intercourse.

(b) In contrast, Haydon et al. analyzed data from the responses of 122,194 adolescents surveyed in the National Longitudinal Study of Adolescent Health. They found that most sexually active adolescents reported either (1) onset of first vaginal intercourse prior to engaging in oral sex or (2) had their first experience with oral sex and their first vaginal intercourse in a similar time frame (within the same year). Only a small subset of adolescents reported that they had engaged in oral sex but had never had vaginal intercourse [12]. Although Haydon et al. only examined data from respondents who engaged in sexual activities with opposite sex partners, Vasilenko et al. also used this survey to look at sexual activity with same sex partners and also found that only a small subset of this population engaged in oral sex only [13].

2. Adolescents consider engaging in oral sex as "having sex."

   (a) In Kaiser's National Survey of Adolescents and Young Adults, two out of every five adolescents did not consider oral sex to be "as big of a deal" as engaging in sexual intercourse [11].
   (b) In 2005, a study conducted with 580 individuals in early adolescence (ninth graders) examined their perceptions about having oral sex as compared to vaginal sex. Respondents in this study perceived oral sex to be less risky than vaginal sex with regard to the health, social, and emotional repercussions. Those adolescents reported that having oral sex would be less likely to be associated with a bad reputation, getting into trouble, feeling badly about themselves, feelings of guilt, less threatening to their own values and beliefs, and a more acceptable sexual activity for people in their age group, as compared to vaginal intercourse [14].
   (c) Only 70 (6%) of adolescents believed that an individual's virginity was still maintained even if that individual had engaged in oral sex [15].

3. Adolescents are aware that individuals may get infected with an STI from having oral sex.

   (a) In Kaiser's National Survey of Adolescents and Young Adults, 20% of respondents did not know that STIs could be transmitted during oral sex. Furthermore, 40% rated oral sex as "safer sex" [11].

Approach to the Medical Visit

History

A careful exposure history can help narrow the extensive differential for symptomatic pharyngitis and can also detect those asymptomatic individuals who may require testing. Oropharyngeal symptoms may also present as a part of systemic disease or as part of a noninfectious syndrome such as allergic rhinitis or gastroesophageal reflux. A broad review of signs and symptoms may be necessary, particularly for those patients who present with chronic or recurrent symptoms. In the

adolescent patient, history should be tailored specifically to this age group. Adolescents should be interviewed about environmental exposures including use of cigarettes, inhalants, and other substances that may irritate the oropharyngeal area. Very importantly, a thorough sexual history should be obtained including history specifically pertaining to oral sex practices.

Although sex is often termed a "risk behavior" for adolescents, one would serve adolescents best to consider sex – including oral sex – a normative behavior, the onset of which frequently occurs during this stage of human development. It is helpful to use this nonjudgmental approach when asking questions regarding oral sex practices and other sexual activities. An additional consideration is the interpretation of the term "sexually active." This can vary greatly from individual to individual depending on their values or knowledge. For example, Jenkins and LeVault surveyed adolescent and young people of ages 15–34 years old who presented for treatment at an urban Emergency Department [16]. Of the 493 participants that were surveyed, approximately 40% of those individuals who denied being "sexually active" also reported that they had engaged in some sexual activity (often, this was oral sex). Thus, practitioners should ask specifically about oral sex and not assume that adolescent patients who state that they are not sexually active have not had oral sex. Many resources offer templates for taking a general sexual history that includes questions about oral sex. For example, the CDC's "A Guide to Taking a Sexual History" provides a possible dialogue that may be used to have this conversation [17]. It is important to assess if the individual's mouth was on their partners' penises, vaginas, and/or anuses. Asking patients if they were the individual giving oral sex, receiving oral sex, or both may aid in stratifying anatomical sites that require screening. It is also important to find out whether patients have used condoms, dental dams, or other products that may reduce the likelihood of STI transmission via oral sex. This dialogue also provides an opportunity to teach patients about how they can reduce the likelihood of acquiring an STI through oral sex. We will discuss prevention later in this chapter.

Because some of the screening guidelines surrounding pathogens that may inhabit the oropharynx can vary depending on the sex of individual's sexual partners, providers should inquire about the sex(es) of individual's sexual partners. However, it is important not to equate an adolescent's stated sexual orientation with the sex of their sexual partners. Adolescents may still be questioning their sexual identity. Additionally, lesbian, gay, bisexual, and queer youth may not have become sexually active yet. And youth who identify as straight and youth who identify as a member of a sexual minority may have sexual contact with members of the same sex or gender and/or the opposite sex or gender [8]. In the Jenkins and LeVault study, about 7% of individuals who self-identified as heterosexual reported engaging in sexual activity with members of the same gender. The article termed these discrepancies activity and orientation misclassification, respectively. Medical jargon, including vague or misconstrued questions about "having sex" or "being sexually active," and the conflation of sexual practices or sexual partners with an adolescent's sexual identity can easily lead to misclassification of information. More importantly, it may result in a clinician misunderstanding a patient's likelihood of acquiring an STI [16].

Physical Exam

Findings on physical exam may also help identify STIs in the oropharynx. Areas that should be examined include the gums, the hard and soft palates, the buccal mucosa, the tongue and area underneath, the tonsils, the anterior and posterior pillars, and the pharynx. Both the anterior and posterior neck should be inspected and palpated to examine for swollen lymph nodes. A good light that is easily manipulated to focus on specific areas is essential for this exam. A tongue blade will likely be required to examine the full mucosa, especially the buccal areas and undersides of the lips. Changes in color including white or reddened areas, ulcers, nodules, or other abnormal lesions should be noted. The patient should be asked to extrude their tongue from the mouth for a full exam including the surface, sides, and underside. Drawing the tongue back in the mouth and having the patient open their jaw wide may provide an adequate view of the pharynx [18]. If not, it may be best to have the patient draw the tongue back into their mouth, partially extend their neck, and loudly say, "ah." Adolescent-aged patients should be able to comply. If a good view is still not obtained, the provider may choose to use a tongue blade to push down on the midsection of the tongue. The blade must be far enough back to be useful but not so posterior that it causes gagging or emesis. The tonsils and pharynx should be examined for erythema, symmetrical position, enlargement, exudate, ulcers, or other lesions.

Prevention

Visits at which oral sex is discussed during history and/or physical exam present an opportunity to educate patients about STIs and oral sex. In addition, information about safer sex precautions can be provided so adolescents can be empowered to reduce their likelihood of being infected with an STI while engaging in oral sex. Use of a protective barrier can reduce transmission. However, most adolescents do not use barrier protection while having oral sex [19]. For adolescents engaging in mouth-to-vagina, mouth-to-vulva, or mouth-to-anus oral sex, latex squares, dental dams may be used to cover the area. If each end of an unrolled condom is cut off and it is then cut lengthwise, it can be made into a rectangle which can then be used as a protective barrier. Each of these barriers can be placed over the area that the mouth will encounter [6]. Although there is no outcome data, latex squares are approved by the FDA for this purpose. None of the other barriers have this designation from the FDA [5]. Attention should be paid to make sure that body fluids do not extend past the barrier and enter the mouth. For mouth-to-penis oral sex, a condom can be used as a protective barrier [6].

Additionally, as discussed previously many adolescents who have had oral sex have also had or will initiate intercourse within the same year. Thus, it is also

important that providers consider expanding the conversation to include pregnancy prevention and contraception, sexual consent, and broader discussion about STIs [20].

Pathogens

Gonorrhea and Chlamydia

Although infections with *Neisseria gonorrhoeae* (gonorrhea) and *Chlamydia trachomatis* (chlamydia) are frequently lumped together when discussed in terms of genital infection, their manifestations as oral or pharyngeal infections are very different from each other. Gonorrhea is commonly considered the STI that is most likely to cause a classic exudative pharyngitis or sore throat. Conversely, while chlamydia is the most commonly reported sexually transmitted infection among young people in the United States, it seems to be far less pathogenic to the oropharyngeal area as compared to genital or extragenital sites (e.g., the rectum and eye). Recently, Chan et al. (2016) published a comprehensive review of 80 studies that examined the prevalence of gonorrhea and chlamydia at different extragenital sites including the pharynx [21]. To further characterize the epidemiology of these infections, the authors further divided the information and looked at infection in women, men who only have sex with women (MSW), and men who have sex with men (MSM). They found broad ranges of prevalence estimates in their review. For pharyngeal gonorrhea, the prevalence was 0–29.6% for women, 0.4–15.5% for MSW, and 0.5–16.5% among MSM. Prevalence of pharyngeal chlamydia was 0.2–3.2% for women, 0–22% for MSW, and 0–3.6% for MSM [21]. When thinking specifically about the adolescent population, other studies seem to indicate that younger age, at least in some populations, confers greater likelihood of acquiring pharyngeal infection. In their retrospective study, Trebach et al. discussed the prevalence of extragenital (including both rectal and oropharyngeal) gonorrhea and chlamydia among patients receiving care at two STI clinics located in Baltimore [22]. Among their population, women who were 18 or younger had almost four times the likelihood of being diagnosed with an extragenital infection as compared with those women older than 18. This pattern was also found among MSW. This finding was not as prominent among the MSM who were involved in the study. However, prevalence of extragenital infection with gonorrhea and chlamydia was higher in the MSM population.

Gonorrhea

Pharyngeal gonorrhea is transmitted to the oropharyngeal area during oral sex. It is most easily transmitted to an individual whose mouth is used on their partner's penis during oral sex but may also be transmitted to an individual using their mouth

on their partner's vagina, though this is less common. Pharyngeal gonorrhea can present with painful pharyngitis which may be accompanied by purulent tonsillitis or lymphadenopathy, particularly along the anterior cervical chain [4, 23, 24]. Isolated erythema of the pharynx may also be present [24]. Rarely, gonorrhea can present with oral infection. Physical exam may reveal very erythematous mucous membranes or a white pseudomembrane. A variety of oral lesions may be found as well but none are specific for gonorrheal infection. Lesions may appear as erythema multiforme or look similar to lesions found with oral HSV or the immunobullous disorders [4, 25].

While consideration of pharyngeal gonorrhea is important, when adolescents present with the above signs and symptoms, it is paramount to remember that most individuals found to have the gonorrhea organism present in the oropharynx are completely asymptomatic. Rarely, oropharyngeal gonorrhea may lead to systemic disseminated infection [23].

Chlamydia

It has been questioned whether chlamydia even causes exudative pharyngitis [26]. While almost all (93–100%) infections are asymptomatic [21], chlamydia can be cultured from the pharynx of sexually active individuals, some of whom present with symptoms of pharyngitis or tonsillitis [4, 27–29]. Still, it seems that chlamydial infection presenting as true exudative pharyngitis is extraordinarily uncommon. Interestingly, there are a few case reports of pharyngeal lymphogranuloma venereum (LGV) resulting from chlamydial infection. In a case series describing four men with pharyngeal LGV in the UK, two were asymptomatic, one had a large tongue ulcer with cervical lymphadenopathy, and the other had pharyngitis and lymphadenopathy [30].

Testing for Oropharyngeal Gonorrhea and Chlamydia

Nucleic acid amplification tests (NAATs) are the preferred test for genital infection with gonorrhea or chlamydia, due to superior sensitivity and specificity. Of note, however, NAATs are technically not FDA approved for use at extragenital sites, and bacterial cultures are the only FDA-approved test for diagnosis. Many laboratories have internally validated the NAATs on extragenital sites. Internal validation should be done in accordance with the Clinical Laboratory Improvement Amendments (CLIA) requirements, and cultures should continue to be run at laboratories that have not validated the NAAT specifically for the oropharynx. In the setting of treatment failures concerning resistance, cultures should also be collected so that samples can be further tested for antibiotic sensitivities [21].

Treatment of Oropharyngeal Gonorrhea and Chlamydia

A substantial portion of pharyngeal infections with gonorrhea and chlamydia will clear on their own. Since an overwhelming majority of pharyngeal infections are indeed asymptomatic and many resolve without treatment, some may wonder about the utility of treating gonorrhea and chlamydia infection at this site. The medical literature presents growing evidence that individuals who have oropharyngeal infection or colonization with gonorrhea and possibly with chlamydia may transmit it to the urethra of their sexual partners during oral sex [21]. Thus, the oropharynx may serve as a reservoir for bacteria and play some role in the propagation of genital infections. It is also thought that gonorrhea or chlamydia harbored in the oropharynx may contribute to development of antibiotic-resistant organisms, as gonorrheal or chlamydial infection at the oropharyngeal site may be harder to eradicate than genital infection [22].

As with genital infections, adolescents should be treated for both gonorrhea and chlamydia if infection with one is found. Treatment for oropharyngeal infections follows the same guidelines as genital infections, with the mainstay of treatment being ceftriaxone 250 mg IM as a single dose plus azithromycin 1000 mg by mouth in a single dose. These should be ideally given at the same time in a supervised setting. Although a test of cure is not routinely recommended, individuals who continue to be symptomatic may require retesting.

Syphilis

It has been established that syphilis can be transmitted between partners during oral sex [5]. This occurs when the partner infected with syphilis has a chancre or single ulcerated lesion. This lesion, which occurs at the site of entry of the spirochete, is teeming with syphilitic organisms and typically occurs on the penis, vagina, anus, or mouth. Adolescents whose oral cavities come in contact with a chancre during oral sex are at risk for getting an oral chancre. Likewise, adolescents who have an oral chancre and perform orogenital or oroanal sex on their partner are at risk of transmitting syphilis to their partners. If it is present in the oral cavity, the chancre is typically on the lip or tongue. Although it is highly infectious, the chancre is typically painless and thus people may be unaware that they have a lesion or may be unconcerned about it.

Most adolescents infected with syphilis never have any oral lesions or symptoms of pharyngitis. However, it is possible for syphilis to have oropharyngeal manifestations at any stage [4, 25]. In primary syphilis, a chancre in the oropharynx can present as a sharply demarginated, round red to brown lesion [4]. Oral manifestations that can present as part of secondary syphilis are variable. Most are nonspecific including shallow ulcers, plaques, and fissures of the tongue. Mucous patches, though rare, may occur and this is the most explicit type of oral lesions that can

occur as part of secondary syphilis. The mucous patch is an oval lesion, often presented as a raised plaque, but can also be ulcerated. A white to gray membrane overlies the patch and the lesion may have an erythematous margin. Multiple mucous patches may be present and they may coalesce [4, 18, 25]. The oral manifestations of tertiary syphilis are uncommon and would be highly unlikely in adolescence, but may include glossitis, areas of destructive "gummas" that may lead to atrophy of the mucosa, or leukoplakia that can progress to squamous cell carcinoma.

Syphilitic pharyngitis may present separately from the disease's oral manifestations. In addition to presenting with symptoms of a "sore throat," case reports of pharyngitis describe accompanying cervical lymphadenitis [31]. This is an uncommon presentation of syphilis. It is important to look for other manifestations of syphilis on physical exam in adolescents who present with persistent pharyngitis and/or cervical lymphadenitis, especially those cases that have been refractory to other treatment.

Identification of syphilitic involvement of the oropharynx requires a high index of suspicion and appropriate serologic testing. Treatment of oropharyngeal syphilis should follow the same guidelines as general treatment of syphilis, dependent upon the stage of infection.

HSV

Although herpes simplex virus type 1 (HSV-1) is the predominant form of herpes virus affecting the lips and oral cavity, it has been well documented that HSV-2, classically associated with herpetic lesions on the genitals, can affect the oropharyngeal area as well. Though HSV-1 is still the predominant type of herpetic infection of the oropharyngeal area, most HSV-1 infections are acquired in childhood [25]. HSV-2 is more likely to be acquired in adolescence or young adulthood and can be transmitted to the oral cavity via kissing or oral sex. Either HSV-1 or HSV-2 can penetrate the epithelial surface of mucosa, especially if there are cuts or abrasions from minor trauma [5].

There are several common clinical presentations related to herpes infection in the oropharyngeal area. Variety in presentation during a single episode relates mainly to whether the episode is the primary infection with the virus or a recurrent presentation. Primary herpetic infection is more likely to present as gingivostomatitis in younger children, characterized by painful vesicles in the oropharynx. These oral lesions may be accompanied by sore throat and fever, but the presentation of sore throat, particularly an isolated pharyngitis, is more common in adolescents with primary infection. In these cases, the posterior pharynx and the tonsils are likely to be the sites affected by herpetic lesions, and the oral mucosa may have no lesions at all [4, 32]. Nakagawa et al. [33] retrospectively examined 32 cases of adolescents and adults (ages 15 years and older) presenting with primary herpetic infection in the oropharyngeal area. Oral lesions were found in only half of their cases. In addi-

tion, lesions were found on the tonsils and posterior pharynx but also on arytenoids, epiglottis, and pyriform sinuses. Sometimes, adolescents with primary infection may even present with a mononucleosis-like syndrome including other symptoms such as headache and fatigue. Recurrent episodes of HSV may present only as the classic "cold sore."

Identification of oropharyngeal HSV is best accomplished by culture or DNA-based testing on swab samples of active lesions. Some oral or intravenous antiviral medications may be beneficial for treatment of severe cases with widespread lesions and severe pain [34].

HPV

More attention has been paid to oropharyngeal HPV infection in recent years, as HPV is increasingly identified as playing a major role in the development of head and neck malignancies. Although much is still unknown about epidemiology, transmission, and course of oral HPV infection, evidence does suggest that HPV can be spread through orogenital or oroanal sexual activity and may be able to be transmitted by deep kissing. The virus is thought to enter the body at the tonsillar epithelium [35, 36]. HPV infection with type 16 has been identified in most oral cancers related to HPV infection. Thus, HPV 16 and the similar HPV 18 are categorized as high-risk HPV types. HPV types 6 and 11 cause noncancerous oral lesions such as warts and thus are deemed "low risk." Oral warts are typically verrucous plaques or squamous papilloma. Less commonly, other oral lesions like epithelial hyperplasia or condyloma acuminatum may appear. The latter usually appears as white papules that grow to form a cobblestone appearance [25].

The majority of HPV infections are asymptomatic. Furthermore, most oral HPV infection is self-limited and clears within one to two years [35, 36]. Most adolescents likely never know that they have HPV infection of the oropharyngeal space. As healthcare providers working with adolescents, it is paramount to work towards administering the HPV vaccine to all patients as it is thought to confer protection from both genital HPV infection and extragenital infection including that of the oropharynx [35].

HIV

Clinical presentation of acute seroconversion syndrome associated with recent HIV infection can present with pharyngitis or even oral ulcers. Aside from this, various opportunistic pathogens, such as HSV, CMV, and *Candida albicans*, may cause pharyngitis or oral lesions in those adolescents and young adults experiencing immunosuppression as a sequelae of HIV/AIDS [25].

Other Pathogens

Other pathogens sometimes discussed within the context of oral sexual activity include bacterial vaginosis, trichomoniasis, vulvovaginal candidiasis, and enteric infections including shigellosis and salmonellosis (most likely transmitted by oroanal sexual activity). Still, it is unclear whether or not oral sex leads to transmission of these infections in a significant number of adolescents [5].

Screening for Sexually Transmitted Infections of the Oropharynx in the Adolescents

Adolescents are covered as a special population in the CDC's screening recommendation for sexually transmitted infections. However, these guidelines are not specific to extragenital or genital infection. For chlamydia and gonorrhea, yearly screening is advised for sexually active women *younger than* 25 years of age. In their 2014 policy statement regarding screening for nonviral STIs in adolescents and young adults, the American Academy of Pediatrics (AAP) recommends routine screening of young women *through* their 25th year. Universal screening for sexually active men in this age group is not recommended by the CDC. However, it is recommended at least annually and possibly more frequently for young men who have sex with men by both the CDC and the AAP. Of note, the AAP guidelines specifically recommend oropharyngeal screening only for gonorrhea. In addition, both the AAP and the CDC recommend that providers working in clinical areas with a high prevalence of chlamydia should consider screening young men as well. In contrast to the CDC, the AAP does recommended rescreening all adolescents who had a positive gonorrhea or chlamydia test 3 months later [37, 38].

For gonorrhea and chlamydia, many individuals who screen positive for these organisms at the oropharyngeal site will not test positive for these organisms when screened only for genital infection [39, 40]. Thus, as discussed earlier in this chapter, a thorough sexual history, including questions specifically pertaining to oral sexual activity, is important step in determining who needs testing specifically of the oropharyngeal area.

Regarding other STIs of the oropharynx in adolescents, syphilis is the only other pathogen for which CDC recommends screening. The CDC guidelines state that pregnant adolescents and young men who have sex with men should be screened for syphilis with the latter group being screened at least annually. AAP guidelines are consistent with these and also mention screening of other individuals who engage in behaviors that may increase their likelihood of being infected with syphilis [37, 38]. Screening for syphilis would involve standard serum testing. There are no screening recommendations at this time for HSV or HPV.

Case Conclusion

Returning to the initial case presentation, we should now be able to confidently answer the questions posed at the beginning of the chapter. It is likely that the initial symptom of sore throat that the student presented with was due to gonorrheal pharyngitis. His pharynx should be examined for purulent discharge, testing should be performed, and he should likely be treated with ceftriaxone and azithromycin. This visit also presents an opportunity for further counseling about STI prevention.

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Chapter 10
Cutaneous Manifestations of Sexually Transmitted Infections

Elizabeth Heller and Robert G. Micheletti

Case Study

A 17-year-old male recently diagnosed with human immunodeficiency virus (HIV), not yet on highly active antiretroviral therapy (HAART), is seen for evaluation of a worsening pruritic rash. He has a history of psoriasis and notes worsening widespread scaling dermatitis over the last 2 months. He was prescribed topical steroids by an outside provider; however, the rash continues to worsen.

The cutaneous exam is notable for diffuse erythema and plaques of thick, sand-like scale. Many linear excoriations are present. A skin scraping is performed and visualized using light microscopy, revealing the presence of mites, ova, and scybala.

Questions for Consideration

- What are common and atypical cutaneous manifestations of STIs?
- What patient factors guide treatment selection?
- When should systemic workup be pursued?

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Localized Viral STIs

Some of the most common STIs in the general population include localized viral skin infections such as human papillomavirus (HPV), molluscum contagiosum, and herpes simplex virus (HSV). These diseases are transmitted via direct contact with infected skin or, potentially, via contact with contaminated objects. These diseases may be chronic or recurrent, as well as painful and disfiguring. They can present atypically in the setting of immunosuppression and may lead to devastating sequelae (e.g., HPV-related cancers).

Genital and mucocutaneous warts result from infection with HPV. There are more than 120 subtypes of HPV, many of which have anatomic predilections and confer different risks to the host; HPV-6 and -11 are associated with benign condyloma acuminata, while HPV-16 and-18 are associated with malignancies of the cervix and anogenital region as well as squamous cell carcinoma of the digits [1]. The diagnosis is typically made clinically; lesions classically are verrucous flat, sessile, or exophytic papules or plaques (Fig. 10.1a), although numerous morphologic variants exist. In immunosuppressed patients, HPV can be diffuse or disseminated, such as the epidermodysplasia verruciformis-like flat warts seen as a marker of advanced HIV infection (Fig. 10.1b). Or extensive, tumorlike masses may form, such as the giant condyloma of Buschke and Löwenstein (Fig. 10.1c), which is an indolent verrucous carcinoma with low metastatic potential [2]. These less common presentations tend to be chronic and refractory to multiple treatment modalities due to the extensive nature of the infection as well as the underlying immunocompromise. Characteristic histopathologic findings can confirm the diagnosis (and help rule out malignancy) if uncertainty exists. Condyloma lata, a genital manifestation of secondary syphilis, is an important alternative diagnosis to consider.

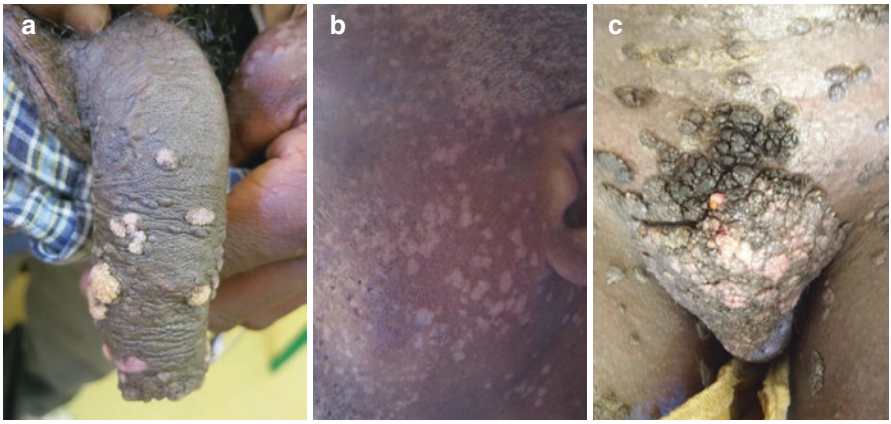

Fig. 10.1 (**a**) Verrucous papules typical of genital warts on the penis. (**b**) Widespread hypopigmented flat warts as a marker for advanced HIV. (**c**) Giant condyloma of Buschke and Löwenstein

Predisposition to HPV infections can be seen in iatrogenic, acquired, or inherited forms of immunosuppression. Syndromic diseases, such as epidermodysplasia verruciformis, WHIM/WILD syndromes, and GATA-2 mutations are characterized by extensive cutaneous verruca. Verrucous carcinoma, an indolent variant of squamous cell carcinoma, can occur within longstanding lesions. While such lesions rarely metastasize, they can be locally destructive and highly infiltrative, forming fistulae and abscesses in the anogenital region. The histologic appearance of such lesions is generally fairly benign, but focal malignant transformation can occur.

Treatment options for HPV infection range broadly, and lesions may self-resolve eventually in immunocompetent patients. Most therapies are destructive, with direct cytotoxic effects on infected cells, while others work by eliciting a host immune response. First- and second-line treatments include cryotherapy, salicylic acid, podophyllin, topical retinoids, and imiquimod. These treatments can be combined or used adjunctively with one another. Podophyllin is potentially teratogenic and should not be used in pregnancy. Cantharidin, derived from the blister beetle, can also be applied topically for its cytotoxic effect. Additional options for recalcitrant warts include topical or intralesional cidofovir, bleomycin, or 5-fluorouracil. Additional physical/destructive modalities include electrocautery, excision, laser ablation, and photodynamic therapy. Such treatments should be performed with care by experienced practitioners given the potential for patient morbidity as well as harm to providers (e.g., inhalation of the plume associated with laser ablation) [3, 4]. Our group has had good experience with intralesional cidofovir (diluted 1:4 with normal saline) for recalcitrant warts on the digits or elsewhere. Adequate pain control, as with a digital block, is essential.

Molluscum

Molluscum contagiosum virus (MCV) is a poxvirus which infects the skin, causing small, firm, pink to pearly papules with central umbilication. Though molluscum is a common infection of children transmitted nonsexually, in adults, the virus is frequently spread via sexual contact and is more commonly seen in the anogenital region (Fig. 10.2a). Molluscum commonly occurs on the trunk, thighs, or face of children and need not trigger suspicion for sexual abuse. The prevalence of molluscum is highest in patients with decreased immunity due to HIV/AIDS, hematologic malignancy, or immunosuppressive medications. In these hosts, lesions can also be atypical in appearance, large or widespread, and refractory to treatment (Fig. 10.2b).

Like genital warts, the diagnosis of molluscum is usually made clinically but can be confirmed histopathologically if HPV or deep fungal infection such as cryptococcus, histoplasmosis, or penicilliosis, which can appear molluscum-like, is suspected. The appearance of the white material which can be expressed from lesions is typical, as are the pathognomonic monomorphic, oval-shaped Henderson–Patterson bodies seen on microscopic evaluation of skin scraping or biopsy

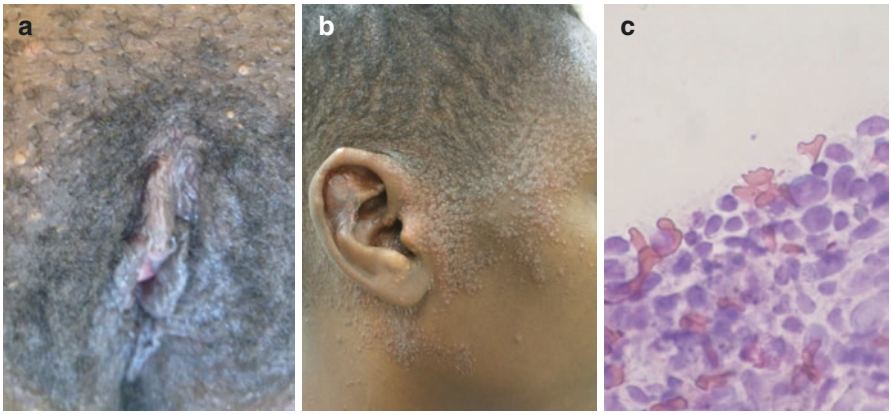

Fig. 10.2 (**a**) Pearly white umbilicated papules of molluscum contagiosum in the genital area. (**b**) Innumerable molluscum lesions in an immunosuppressed patient with adult T-cell leukemia/lymphoma. (**c**) Henderson–Patterson bodies, monomorphic oval inclusions of molluscum as seen on Tzanck smear

(Fig. 10.2c). Treatment options for MCV overlap significantly with genital warts and include cryotherapy, cantharidin, topical retinoids, and imiquimod. Lesions may be manually expressed with curettage or extraction, which leads to their resolution; expressed material contains active virus and may be infectious [5].

Genital Ulcers

Many sexually transmitted infections present with genital ulceration, making the differential diagnosis for these lesions quite broad [6], as shown in Table 10.1. Appropriate diagnosis and treatment are important due to the morbidity associated with these diseases. Genital ulcers have also been shown to facilitate the transmission of other STIs such as syphilis and HIV, themselves leading causes of morbidity and mortality worldwide.

Herpes Simplex Virus

Genital herpes simplex virus (HSV) classically presents with grouped vesicles on an erythematous base. Tingling or burning may precede the appearance of lesions in both primary and recurrent infection. In primary infection, affected individuals may also experience malaise, painful lymphadenopathy, and fever prior to the onset of cutaneous findings. Subsequent reactivations tend to occur in the same area.

Table 10.1 Differential diagnosis and distinguishing features of genital ulceration

Diagnosis	Distinguishing features	Diagnostic method
Herpes simplex virus	Punched-out ulcerations or vesicles in grouped distribution; form a "scalloped" border when lesions coalesce	HSV PCR Tzanck smear
Chancroid	Well-demarcated, painful, purulent ulceration; unilateral ulcerating lymphangitis with erythema	Smear showing *H. ducreyi* ("railroad track pattern") culture
Lymphogranuloma venereum	Transient mucosal ulceration followed by rapidly expanding nodules ("buboes") and sinus tract formation; unilateral lymphadenopathy	PCR or nuclear amplification assay to *C. trachomatis*
Granuloma inguinale	Papules coalescing into large well-defined beefy red ulcers with foul-smelling drainage	Intracellular organisms ("Donovan bodies") from smear of active lesion with Giemsa stain
Syphilis (primary)	Painless indurated ulcer on the penis or vulva, typically solitary	Skin biopsy, immunohistochemical stain Darkfield microscopy Anti-treponemal antibodies (RPR, VDRL, FTA-ABS) – less sensitive in primary disease
EBV (Lipschutz ulcer)	Large, painful ulcers with heaped-up borders, predominantly affecting adolescent females; oral aphthae, fever, lymphadenopathy	EBV PCR Rule out other infectious causes of genital ulcer
CMV	Chronic perianal or perineal ulceration, in the setting of immunosuppression	CMV PCR or serologies Skin biopsy ("owl's eye" appearance)
Cutaneous Crohn's	Perineal or perianal ulcers, fistulae, skin tags, sinus tracts; associated gastrointestinal manifestations	Skin biopsy Workup for IBD including colonoscopy, fecal leukocytes, lactoferrin
Hidradenitis suppurativa	"Black heads," acneiform papules, abscesses, and draining sinus tracts in the groin, axillae, under the breasts; chronic, recurring, and bilateral	Clinical, not to be confused with folliculitis/furunculosis, staph abscess, etc.
Fixed drug eruption	Well-defined erythematous to hyperpigmented round or oval plaque; recurs repeatedly in the same location(s) with medication use	Skin biopsy Cessation of possible trigger (e.g., NSAIDs, pseudoephedrine, antibiotics, others)
Behcet disease	Recurrent oral and genital ulcerations associated with uveitis or retinal vasculitis, pathergy, erythema nodosum, papulopustular lesions, or acneiform papules	Clinical; exclusion of alternative diagnoses Skin biopsy may show neutrophilic infiltrate and vasculitis

HSV has two serotypes: HSV-1 is typically acquired via direct contact with infected secretions before the age of 10, while HSV-2 is acquired after puberty through sexual contact. While both serotypes can cause herpetic genital lesions, HSV-2 is the leading associated serotype worldwide. Following primary infection of mucocutaneous sites, the virus replicates and becomes latent within the dorsal root ganglia. Reactivation occurs with physiologic stress, localized injury, or impaired cell-mediated immunity.

In the setting of immunocompromise, symptom duration and viral shedding may be prolonged. The presentation of HSV in such individuals is frequently atypical, chronic, or widespread. Permutations of the classic 1–2-mm vesicle include hemorrhagic vesicles, pustules, erosions, and crusts. As multiple round lesions coalesce, they create a scalloped border which is typical in chronic HSV infection (Fig. 10.3a). Symmetric lesions on opposing sides of a body-fold area are referred to as "kissing lesions" and are another clue to HSV infection (Fig. 10.3a). In unusual cases, linear painful fissures can occur in body-fold areas like the intergluteal cleft, forming the "knife-cut ulcer" of chronic HSV (Fig. 10.3b). A similar process may occur on the tongue. Tumorlike masses known as verrucous HSV may also occur. Such atypical presentations generally occur only in the setting of profound immunosuppression, such as in advanced HIV. Vesicles and erosions may also become disseminated over a large part of the skin surface (this is referred to as "eczema herpeticum" or "Kaposi varicelliform eruption") in patients with dysfunctional skin barrier function and/or immunocompromised (e.g., atopic dermatitis, cutaneous T-cell lymphoma, and certain genetic skin conditions). Such patients are at risk for systemic infection, both viral and bacterial. The possibility of dissemination of HSV to the liver, lungs, and central nervous system should be considered in at-risk immunocompromised patients.

The diagnosis of HSV infection is usually made clinically but can be confirmed via various testing modalities, if necessary. Tzanck smear can provide diagnostic confirmation in real time for those with access to a microscope but cannot differentiate HSV from VZV. PCR is widely available, with results typically available within 1 day. Viral culture can be done, but the results will generally not be available for several weeks – while diagnostic, this modality is therefore not useful for guiding

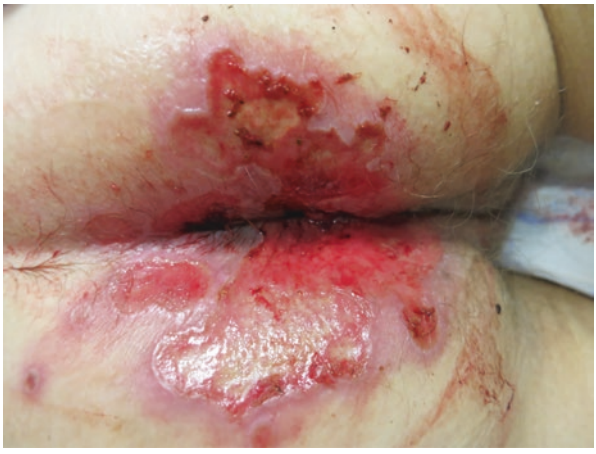

Fig. 10.3 Chronic herpes simplex virus infection; a scalloped border results from coalescing individual round lesions, while skin-to-skin contact results in symmetric "kissing" lesions

therapeutic decision-making. Finally, in some atypical presentations, immunostaining of skin biopsies for HSV-1 or HSV-2 can help secure the diagnosis.

Treatment options include oral antiviral agents such as acyclovir, valacyclovir, or famciclovir, prescribed in short courses for flares or as daily suppressive therapy. For severe or disseminated infections, IV acyclovir is the mainstay of therapy and should be continued until lesions are crusted over. If acyclovir resistance is suspected (failure to respond to appropriate therapy after 7–10 days is a useful clue), treatment with foscarnet or cidofovir should be considered. Because the toxicities of these medications may be limiting, alternative means may be considered. A compounded topical cidofovir (e.g., 1% ointment) can be effective for superficial lesions. Verrucous, mass-like HSV may respond to intralesional cidofovir [7].

Chancroid

Chancroid is another infectious cause of genital ulcers. It is more common in developing countries, although outbreaks have been reported in the USA. The causative organism is *Haemophilus ducreyi,* a small gram-negative anaerobic bacillus transmitted via sexual contact with an infected partner. Men are roughly ten times more frequently diagnosed than women because women are more likely to be asymptomatic carriers. Clinically, chancroid typically starts with an inflamed papule that progresses to a pustule and over time breaks down to form a painful, sharply demarcated ulcer with a purulent base. In men, lesions are located on the internal or external surface of the prepuce, coronal sulcus, or frenulum. In women, lesions occur within the introital area and may be only mildly symptomatic. Evaluation for involvement of the cervix and vaginal wall should also be considered. Painful inguinal lymphadenitis, which is typically unilateral, may also occur. The lymphadenitis may rupture, leading to inguinal ulceration.

A smear of the exudate from chancroid lesions may reveal clusters or lines of coccobacilli (in "school of fish" or "railroad track" pattern) of *H. ducreyi*, although this finding is not specific. The reference standard for diagnosis is isolation of the causative bacteria on appropriate media. Chancroid is readily treated with antibiotics. Single-dose azithromycin or ceftriaxone may be appropriate for immunocompetent hosts. Immunosuppressed patients require a longer treatment course and close monitoring for delayed healing or treatment failure. All recent sexual partners (within 10 days prior to the onset of patient symptoms) should be examined and treated as well [8].

Lymphogranuloma Venereum

Lymphogranuloma venereum (LGV) is a chronic sexually transmitted infection caused by *Chlamydia trachomatis* serovars L1–L3. It is endemic to the Caribbean, East and West Africa, South America, and South/Southeast Asia, although more recently outbreaks in Europe and the USA have been reported. It occurs more commonly in densely populated areas. Individuals with concurrent HIV are particularly at risk.

Half of infected individuals develop a transient erosion resembling herpes at the site of exposure, typically a mucosal surface of the genitalia or rectum. This erosion is typically accompanied by a local lymphadenitis. Concomitant cervicitis, urethritis, or proctocolitis can also occur. In the secondary stage of the disease, unilateral lymphadenopathy accompanied by erythema occurs (known as "inguinal syndrome"), along with firm buboes that rapidly expand and form sinus tracts. These may eventually rupture, drain purulent material, and spontaneously heal. Relapse occurs in 20% of untreated patients. Ano-genito-rectal syndrome is a complication of LGV in which proctocolitis and hyperplasia of the intestinal lymphatic tissue leads to local abscesses with anal fistulae, rectal strictures, and stenoses. Systemic symptoms are rare but can include meningitis, hepatitis, or arthritis. LGV is diagnosed via PCR or nucleic acid amplification assay. Treatment with doxycycline is curative; however, surgical intervention may be needed for large buboes. Any sexual partners within 30 days of onset of symptoms must also undergo treatment [9].

Granuloma Inguinale

Granuloma inguinale is commonly classified as an STI, although it can also occur in individuals who are not sexually active. This disease most commonly occurs in young adults, ages 20–40, and is endemic to South Africa, India, Papua New Guinea, and Australia [10]. The causative agent is an intracellular bacterium, *Klebsiella (Calymmatobacterium) granulomatis*. Clinically, lesions begin as small papules or nodules that progress to well-defined beefy red ulcers. The ulcers are typically painless or mildly painful and may bleed or drain a foul-smelling exudate. Typical locations include the glans penis, frenulum, or coronal sulcus for men and the vulva for women, although extragenital involvement can occur in the bone, oral cavity, or abdomen of both sexes.

The diagnosis is typically clinical. The presence of Donovan bodies – collections of intracellular bacteria – can be seen on smears of dermal scrapings stained using Giemsa, Wright, or Leishman stains. This characteristic finding has given rise to the alternative disease name "donovanosis" but should not be confused with *Leishmania donovani*, the intracellular parasite that causes cutaneous leishmaniasis. Patients with granuloma inguinale are typically treated with a minimum 3-week course of doxycycline that should be extended until all lesions are healed. Alternative antibiotics such as trimethoprim–sulfamethoxazole, azithromycin, and chloramphenicol may be used based on local availability. Relapses can occur up to 18 months following initial treatment, even if successful [11].

Other Causes of Genital Ulcers

The differential diagnosis for genital ulcers is broad. Syphilis can clinically resemble any of the above STIs in primary or secondary form and will be discussed in more detail later in this chapter.

Additional infectious etiologies may include Epstein–Barr virus (EBV), the most commonly reported causative agent of Lipshütz ulcers (Fig. 10.4). These lesions are typically large, painful ulcerations with heaped borders that occur predominantly in adolescent females who are frequently not sexually active. Associated fever, malaise, lymphadenopathy, and oral aphthae are typical [12].

CMV is another virus associated with chronic perineal ulcerations; this etiology of genital ulcer should be considered in immunosuppressed patients, such as those with HIV/AIDS or hematologic malignancy, especially if the ulcer fails to respond to standard therapy for HSV.

Inflammatory causes of genital ulcers include Crohn disease, which can cause oral, genital, or rectal aphthae, painful linear ulcers of body folds ("knife-cut sign"), abscesses, fistulae, and sinus tracts in the perineal and/or perianal area.

Hidradenitis suppurativa may be improperly diagnosed as a sexually transmitted infection by those unfamiliar with the presentation of the disease. Open comedones or "black heads," acneiform nodules, draining abscesses, and sinus tracts may involve the axillae, groin, inframammary area, or other locations (Fig. 10.5a, b). Though pain, erythema, and purulent drainage are key features of the condition, it is not an infectious disease but rather a multisystem inflammatory condition which may be associated with increased cardiovascular risk, metabolic syndrome, inflammatory arthritis, and inflammatory bowel disease, as well as high rates of depression and anxiety. The most commonly affected demographic group is women ages 20–29 [13]. Such patients frequently present to urgent care, the emergency department, obstetrics/gynecology, primary care, and STI-focused health clinics.

Behcet disease is frequently considered in the differential for patients with recurring genital ulcerations (Fig. 10.6). Criteria for this chronic, relapsing inflammatory disease include recurrent oral ulcerations (at least three episodes per year) and two of the following, in the absence of an alternative clinical explanation: recurrent genital ulcerations, uveitis or retinal vasculitis, positive pathergy test, or additional skin manifestations including erythema nodosum, papulopustular lesions, or acneiform papules.

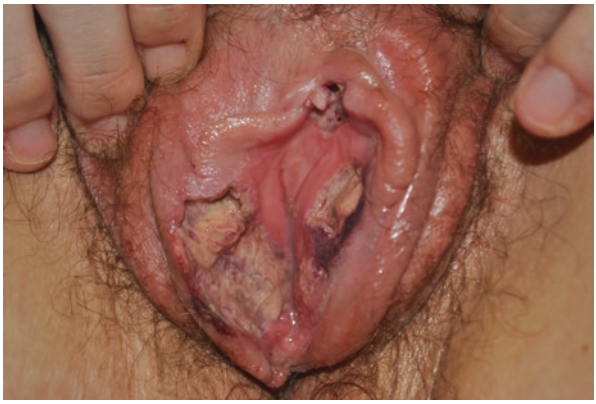

Fig. 10.4 Painful, swollen, and friable Lipshütz ulcer involving the labia of a young woman

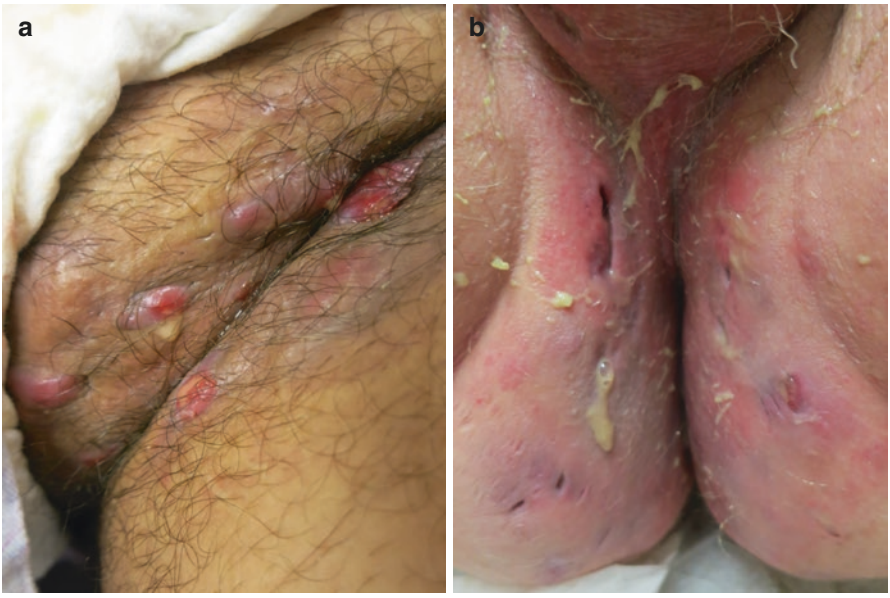

Fig. 10.5 (**a**) and (**b**) Painful acneiform nodules, abscesses, and sinus tracts with purulent drainage in hidradenitis suppurativa

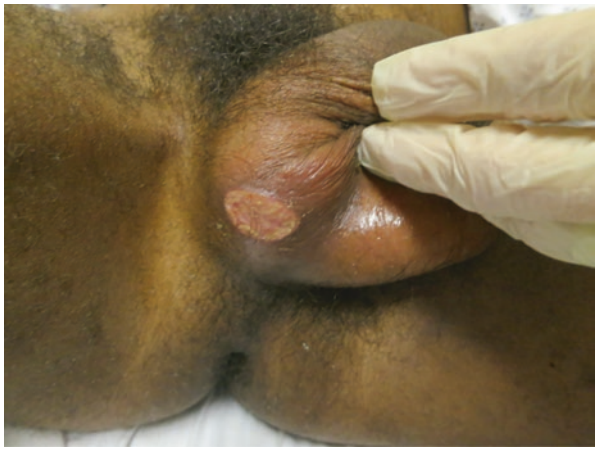

Fig. 10.6 Scrotal ulcer typical of Behcet disease

Systemic Diseases

Syphilis

Cutaneous manifestations of syphilis are quite varied, consistent with its moniker "the great imitator." Because the clinical presentation differs depending on the stage

of disease, patient immune status, coinfections, and spirochete burden, a high index of suspicion is needed for accurate diagnosis.

Primary syphilis is typically characterized by an asymptomatic papule that progresses over days to a solitary round or oval indurated ulcer, or chancre. Chancres occur at the site of inoculation, which includes the glans, coronal sulcus, and foreskin for men and labia, cervix, and vaginal fourchette for women. A regional lymphadenopathy is associated. Due to the asymptomatic nature of these ulcers and their often inconspicuous location, resolution may occur in a few weeks without detection. Atypical primary chancres have been reported, further clouding diagnosis; examples include multiple and/or painful chancres, extragenital location (Fig. 10.7a), and lack of ulceration. Skin biopsy demonstrates a diffuse lymphohistiocytic dermal infiltrate with numerous plasma cells. Warthin–Starry or immunohistochemical staining can be used to visualize spirochetes within the lesion. Darkfield microscopy of fluid from the surface of a chancre is the most sensitive and specific method of diagnosis at this stage, as anti-treponemal antibodies are less reliable.

If syphilis remains untreated, it may progress to the secondary stage in weeks to months. Mucocutaneous manifestations are more varied at this stage and may be

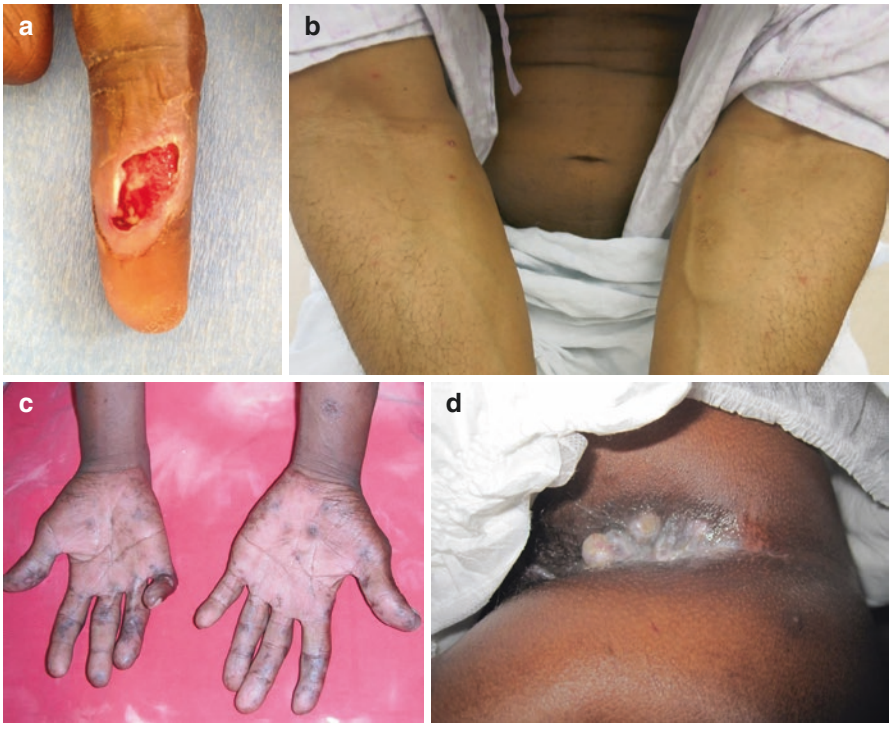

Fig. 10.7 (**a**) Primary syphilitic chancre in an atypical extragenital location on the finger. (**b**) and (**c**) Red-brown, hyperpigmented, thin, and scaling papules on the trunk, extremities, and palms in secondary syphilis. (**d**) Condyloma lata in secondary syphilis

associated with prodromal or focal neurologic findings. The most common cutaneous manifestation is a diffuse asymptomatic papulosquamous eruption composed of pink or red-brown papules with fine scale, ranging from 2 to 20 mm in diameter (Fig. 10.7b, c). Additional cutaneous findings include annular plaques with central hyperpigmentation on the face and raised, indurated nodules or plaques. A generalized non-scarring, patchy, or "moth-eaten" hair loss can occur. Oral manifestations include small superficial mucosal aphthae, large grey plaques on the oral mucosa, and 'split papules' – fissured papules at the edges of the lips which can be confused with angular cheilitis. In the anogenital area, secondary syphilis can present as condyloma lata (Fig. 10.7d), which are flesh-colored to hyperpigmented verrucous papules coalescing into plaques. These may be confused with HPV, so a complete skin exam for additional clinical clues is important in differentiating these entities. A rare condition, lues maligna ("malignant syphilis"), has been described primarily in immunocompromised patients; this manifests as disseminated ulcerated plaques that may resemble the primary chancre.

Secondary syphilis is typically diagnosed via serologic testing. Skin biopsy may also be helpful in confirming the diagnosis when in doubt. Histopathologic findings include elongated epidermal ridges and deep lymphohistiocytic infiltrate with plasma cells. Older lesions may show granulomas that can be differentiated from sarcoidosis by the presence of plasma cells. Immunostains may be used, as above. If left untreated, these manifestations typically resolve in weeks to months, but relapse occurs in up to 25% of patients within 1 year [14].

Classically, evolution of the disease includes an asymptomatic latent period followed by a tertiary phase in approximately one-third of untreated patients. Cutaneous manifestations may appear months to years after initial infection. Gummas present as arcuate plaques or nodules that can ulcerate, healing over weeks to months with involution and scar. If solitary and subcutaneous, a lesion may resemble a cold abscess. Lesions typically come and go at any location on the skin or oral cavity, including the tongue. They may be locally destructive and can also originate in the bone, CNS, myocardium, or great vessels. In tertiary syphilis, nontreponemal serologic testing usually yields high titers. Skin biopsy may show a granuloma with or without necrosis, resembling tuberculosis but differentiated by the presence of plasma cells. Spirochetes are no longer present at this stage.

Gonorrhea

Gonorrhea, an STI caused by *Neisseria gonorrhoeae*, may also manifest in the skin. Recognition of these findings is important for early diagnosis, which may reduce the risk of serious sequelae, including infertility, chronic pelvic pain, and ectopic pregnancy. The clinical presentation and symptomatology of gonorrhea vary based on the site of infection and organism strain. Ninety percent of men experience urethritis with dysuria and purulent discharge, which can ascend to involve the epididymis, prostate, or bladder. These symptoms can resolve in 6 months without treatment.

In women, approximately half will experience dysuria, menorrhagia, and purulent discharge after infection, typically of the endocervical canal, and can eventually progress to pelvic inflammatory disease (PID). The rectum can also be involved in both genders, resulting in proctitis, tenesmus, and rectal bleeding and/or discharge. Oral ulcerations or mucosal erythema can occur in pharyngeal infections.

Cutaneous manifestations of primary gonorrhea are uncommon. Small erythematous pustules, indurated furuncles, abscesses, or punched-out erosions or ulcerations can occur on the genitalia. Extragenital lesions such as digital pustules, abscesses, ulcerations, and suprapubic ecthyma have been reported in areas of prior trauma. Secondary cutaneous involvement includes edema and erythema of the urethral meatus, glans, or foreskin in men. Women may infrequently develop small pustules or tender nodules on the genital skin, resulting from spread of infection. Infection of the specialized glands in the genital skin can present as inflammatory papules or pustules in both genders.

If gonorrhea remains untreated, dissemination can occur, causing a triad of oligoarthritis, tenosynovitis, and dermatitis, along with fever and malaise. Skin involvement includes pinpoint hemorrhagic macules that can evolve into necrotic or ulcerated pustules, papules, or vesicles. These may be transient, lasting only 3–4 days even without treatment. Angulated violaceous plaques representing an embolic septic vasculitis ("purpura fulminans") may occur, especially involving distal sites. Histopathologic features of cutaneous gonorrhea are nonspecific, making skin biopsy less useful for diagnosis [15].

Human Immunodeficiency Virus (HIV)

HIV is associated with myriad cutaneous manifestations with varying morphologies [16, 17], as summarized in Table 10.2. Primary infection with HIV is associated with a generalized morbilliform eruption involving the face and trunk, along with fever and malaise as part of the acute retroviral syndrome. Ulcerations of the oral or anogenital mucosa have also been reported. Given the nonspecific findings associated with this syndrome, a high degree of clinical suspicion is needed. Patients are viremic and highly infectious during this period.

At lower CD4 counts, patients are at risk for numerous dermatologic complications, including exacerbation of preexisting primary skin conditions such as psoriasis, atopic dermatitis, or seborrheic dermatitis, with some patients even becoming erythrodermic (>80% body surface area involved). HIV-positive patients may also develop fairly characteristic dermatologic manifestations associated with low nadir CD4, like pruritic papular eruption of HIV involving the trunk, eosinophilic folliculitis involving the head and neck, and photosensitivity eruption or hyperpigmentation affecting sun-exposed areas.

Individuals with advanced HIV are also at risk for various opportunistic infections of the skin, including common and uncommon bacterial, viral, fungal, and mycobacterial infections such as Staph impetigo, extensive HPV or molluscum,

Table 10.2 Selected cutaneous manifestations of HIV

CD4+ count	Erosions/ulcers	Papules/pustules	Nodules/abscesses	Erythema/scale	Pigmented lesions	Mucosal lesions
>500	Herpes simplex Porphyria cutanea tarda Syphilis	Acute retroviral syndrome Drug eruption Staph folliculitis Scabies	Staph furuncle Syphilis	Tinea Seborrheic dermatitis Chronic actinic dermatitis Syphilis	Zidovudine-associated melanonychia	Oral hairy leukoplakia Vaginal candidiasis Herpes simplex Acute retroviral syndrome
<500	Herpes zoster	HPV/warts	Kaposi sarcoma	Psoriasis (severe, refractory)	Eruptive atypical melanocytic nevi Melanoma	Thrush Kaposi sarcoma
<250	Herpes simplex (disseminated)	Eosinophilic folliculitis Molluscum (extensive) Disseminated: Cryptococcus Histoplasmosis Coccidioidomycosis Non-melanoma skin cancer	Bacillary angiomatosis Tuberculosis Botryomycosis Cutaneous T-cell lymphoma Non-melanoma skin cancer (advanced)	Seborrheic dermatitis (exuberant) Crusted scabies	Photodistributed hyperpigmentation	Necrotizing ulcerative gingivitis/periodontitis
<50	HSV (large, chronic) CMV	Papular pruritic eruption Molluscum (giant) Aspergillosis	Atypical mycobacteria (avium, chelonae) Aspergillosis	Acquired ichthyosis Pityriasis rubra pilaris (type VI)	Photodistributed hyperpigmentation	Major aphthae

disseminated cryptococcus, or cutaneous manifestations of tuberculosis. Various malignancies, including Kaposi sarcoma, HPV-associated squamous cell carcinoma, and cutaneous lymphoma may present in the skin. Patients with HIV/AIDS are also at 100- to 1000-fold increased risk of cutaneous drug eruptions, including severe, life-threatening reactions like Stevens–Johnson syndrome/toxic epidermal necrolysis [18]. Finally, immune reconstitution inflammatory syndrome (IRIS) may cause an exacerbation or flare of underlying skin disease in patients with very low CD4 counts undergoing count recovery in the weeks to months following initiation of antiretroviral therapy.

Parasites

Pubic Lice

Pthirus pubis (crab lice, pubic lice) are small mites with a short, wide body and serrated claws which enable attachment to the hair shaft. Infestation presents with pruritus localized on the pubic region following exposure to an infested partner. Mites and/or nits may be visible to the naked eye and can mimic hemorrhagic crusts at the base of the hair shaft. Perifollicular erythema and excoriation, as well as evidence of secondary infection and lymphadenopathy, may be noted. Slate-grey to bluish irregular macules on the trunk and thighs, called macula caerulea, are evidence of chronic infestation. Mites can travel to other hair-bearing sites including the scalp, eyebrows, eyelashes, beard, and axillae. Thus, a thorough examination of hair-bearing areas is recommended. Differential diagnosis includes scabies and arthropod bite reaction, as well as white piedra and trichomycosis pubis. Visual identification of the pubic louse or nits is diagnostic. Skin biopsy is usually unhelpful given its nonspecific inflammatory pattern. Treatment is with topical permethrin. Perianal and eyelash involvement may necessitate oral ivermectin.

Scabies

Infestation with the mite *Sarcoptes scabiei* var. hominis presents with pruritic, crusted to keratotic papules favoring body-fold areas and creases/seams where clothing is tight against the skin. Inflammatory papules and burrows may be seen in the finger and toe webs (Fig. 10.8a), on the wrists, in the axillae, on the breasts, waistline, groin, and penis. The scalp and face are typically spared. Crusted or "Norwegian" scabies occurs in the setting of immunosuppression (Fig. 10.8b). This entity is characterized by generalized, yellow-white, sand-like crusted plaques that continue to favor body fold areas but can also involve the scalp and face. Such patients have a high mite burden, so they and their environment are highly conta-

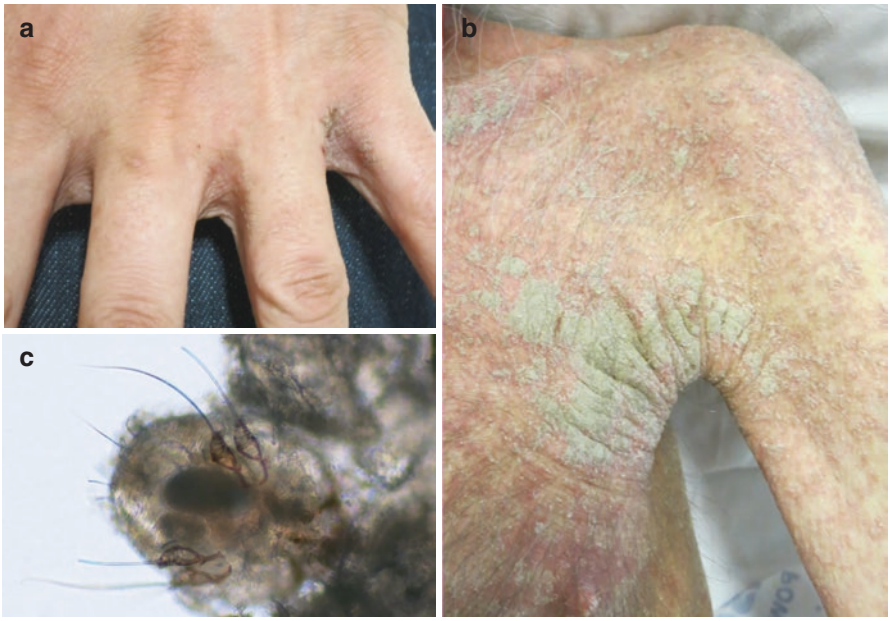

Fig. 10.8 (**a**) Crusted papules and burrows in the finger web spaces typical of scabies infestation. (**b**) Thick, sand-like scale, most prominent in body-fold areas, in crusted scabies. (**c**) Scabies mite and oval scybala

gious, necessitating sufficient infectious control precautions [19]. Secondary bacterial infection of excoriated or eroded areas may occur.

A skin scraping from an affected area (focusing on the "hot spot" areas listed above) should be obtained and examined under light microscopy with mineral oil preparation. The identification of mites, ova or feces (scybala) confirms the diagnosis (Fig. 10.8c). Topical permethrin from the neck down is the first-line agent for treatment; oral ivermectin is an alternative. Recommended treatment for crusted scabies includes daily permethrin and repeated doses of oral ivermectin until clearance of the infestation is demonstrated on skin scraping; 1 month of treatment is not uncommon for such patients. Post-scabetic itch can persist for 2–4 weeks following appropriate treatment and is not indicative of active infection. Topical steroids and moisturizers can bring itch relief in such patients.

Other Nonsexually Transmitted Genital Dermatoses

When confronted with a rash or lesion on the genitalia, it is natural for patients and providers to worry about STIs. Yet, there are numerous noninfectious dermatoses which may occur on the genitals, in the groin, or in the perianal area. It is common

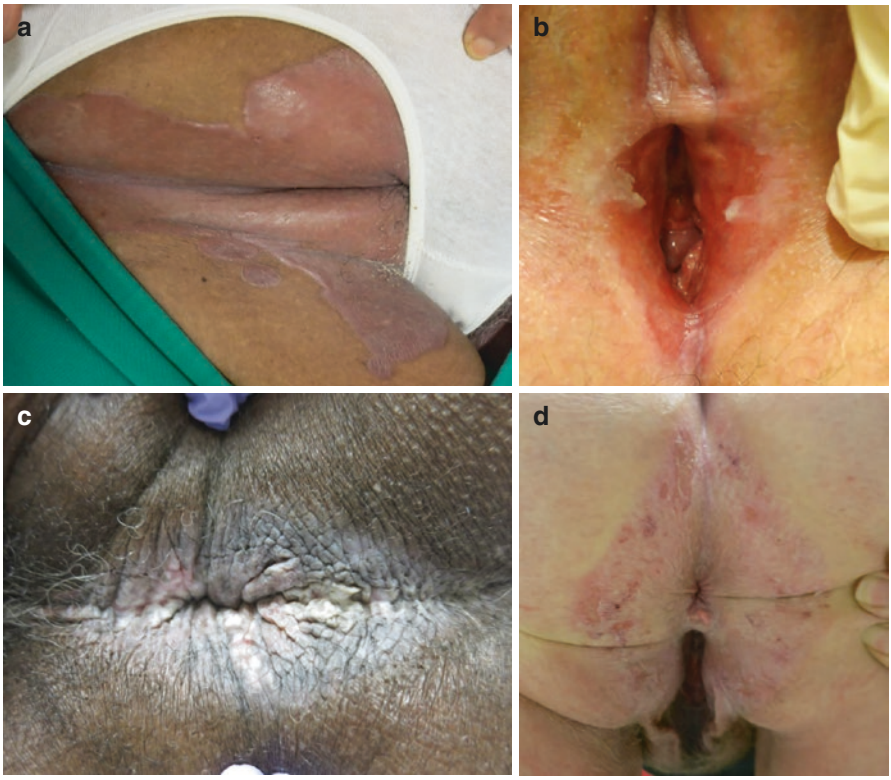

Fig. 10.9 (**a**) Inverse psoriasis with well-defined smooth, shiny plaques in intertriginous areas. (**b**) Erythema, leukoplakia, and atrophy of the labial mucosa with alteration of normal anatomy in lichen sclerosus et atrophicus. (**c**) Lichenification and accentuation of skin markings in the perianal area in lichen simplex chronicus. (**d**) Symmetric erythema and erosions due to allergic contact dermatitis to propylene glycol in cleansing wet wipes

for such processes to be managed inappropriately, leading to delays in therapy or exacerbation due to incorrect treatment.

Some, like psoriasis (Fig. 10.9a), are common skin conditions which frequently affect other areas of the body but which may look different in the genital area. So-called "inverse" psoriasis (Fig. 10.9) occurs in body-fold areas. It is well defined and has a glossy red or eroded appearance, lacking the scale typically seen in other areas of the body due to chronic moisture.

Lichen sclerosus et atrophicus (Fig. 10.9b) is an inflammatory dermatosis of the genital and extragenital skin which results in erythematous and white, atrophic, scar-like plaques associated with itching, pain, and, ultimately, adhesions, functional limitations, and destruction of normal genital anatomy. Because of lack of awareness of the condition, it is commonly mistaken for genital yeast infection and treated with antifungals when potent topical steroids and other anti-inflammatory agents are instead preferred.

Chronic rubbing and scratching results in thickening and hyperpigmentation of the skin, which accentuates skin markings, resulting in a verrucous, or wartlike appearance. This process—lichen simplex chronicus (Fig. 10.9c)—commonly affects the scrotum, vulva, and perianal area and responds to topical steroids.

Personal-cleansing products such as wet wipes and scented panty liners, as well as various over-the-counter home remedies (e.g., tea tree oil, witch hazel), are common causes of irritant or allergic contact dermatitis (Fig. 10.9d). A thorough history is necessary to identify and stop causative agents.

Case Conclusion

The patient's presentation is consistent with crusted scabies, a hyperinfestation of the mite *Sarcoptes scabiei* var. hominis in the setting of immunosuppression. The key feature is the presence of thick, tan, sand-like crusted plaques in a susceptible patient; visualization of mites, ova, or scybala (feces) confirms the diagnosis.

The patient receives both oral ivermectin and topical permethrin until clearance of the mite is confirmed via skin scraping. The patient's close contacts are treated with ivermectin prophylactically.

It is important to recognize ways in which the clinical appearance of crusted scabies differs from that of psoriasis, seborrheic dermatitis, and other dermatoses which may worsen in the setting of immune dysregulation in advanced HIV. In this case, the thick, tan, sand-like scale of crusted scabies is virtually pathognomonic.

Cutaneous manifestations of sexually transmitted infections can be the initial indication of important systemic disease processes and/or markers of advanced infection or immunocompromise. Even if limited to the skin, cutaneous symptoms may disproportionately impact quality of life through pain, itch, drainage, social stigma or isolation, and sexual dysfunction. Importantly, cutaneous STIs may also mimic the appearance of noninfectious diseases, or vice versa, thereby delaying diagnosis and resulting in inappropriate treatment. Familiarity with the typical and atypical presentations of cutaneous STIs and their mimickers is therefore critically important for the practicing pediatrician, adolescent medicine specialist, internist, gynecologist, and infectious disease specialist. Early and correct diagnosis of these conditions may improve the long-term health of patients.

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Part III
Major Pathogens

Chapter 11
Syphilis in Adolescents and Young Adults

Emma Goodstein and Kimberly Workowski

Case Study

A 17-year-old male presented to the emergency room in a large public hospital, with a chief complaint of sore throat. He was in his usual state of health until 2 weeks prior to presentation, when he noticed the development of bilateral enlarged "bumps" in his groin. A few days later, he developed a sore throat and more swollen glands in his neck, particularly on the right. He initially presented to an urgent care clinic near his home, where a rapid streptococcal antigen test was negative, and he was presumed to have a viral upper respiratory illness. However, his symptoms progressed – leading to the current presentation in the emergency department. Physical examination was notable for temperature of 102 degrees F, right-sided unilateral tonsillitis, 3–4 cm ipsilateral anterior and posterior cervical lymph nodes, and an erythematous macular rash over his trunk and upper extremities, with involvement of the palms and soles. A careful history elicited mention of a painless ulcer near the patient's anus that persisted for several days approximately 2 months prior to presentation. He also reported occasional episodes of unprotected sexual encounters with male partners (Figs. 11.1 and 11.2).

Questions for Consideration

- What diagnostic tests should be performed?
- What risk factors for syphilis does this patient have?
- What preventative screening should the patient receive in the future?

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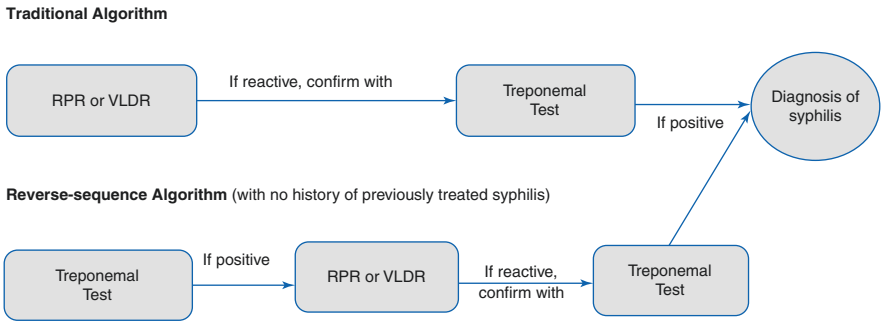
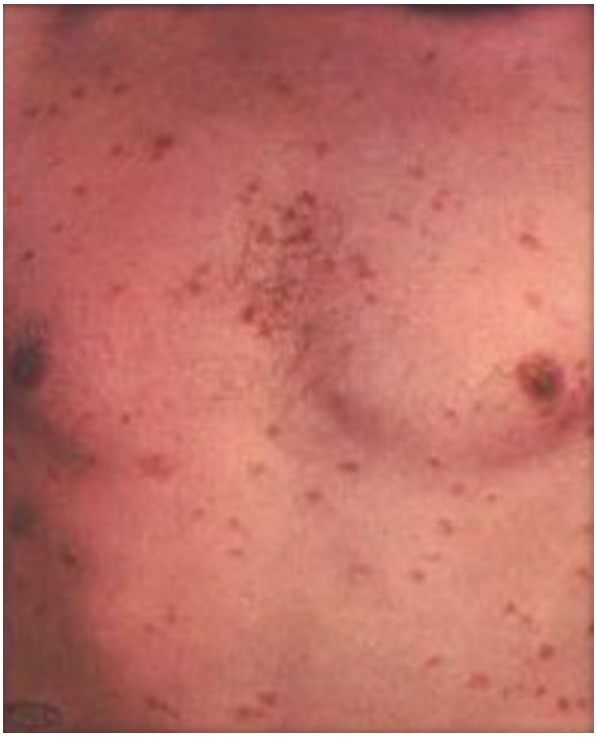


Fig. 11.1 Maculopapular rash over trunk

Fig. 11.2 Tonsillitis



Epidemiology

Less than 20 years ago, infectious syphilis was on the verge of eradication in the United States. The Centers for Disease Control and Prevention (CDC) published a "National Plan to Eliminate Syphilis from the United States" in 1999, and less than 10,000 cases of primary and secondary syphilis were reported the following year [1]. Since that time, however, syphilis rates have increased dramatically in the United States [2]. In 2015, 23,872 new syphilis cases (including all stages) were

reported in the United States – more than doubling in the 15 years since the CDC's elimination plan was proposed [3].

Rates of syphilis are higher among men, especially men who have sex with men (MSM). Men accounted for 90.3% of all primary and secondary syphilis cases in 2015 [3]. New cases are diagnosed with increasing frequency among young adults; the highest rates of primary and secondary syphilis are now found among young men ages 20–29. This represents a marked epidemiologic shift over the past 10 years; previously, syphilis was much more common among middle-aged men (ages 35–59). Racial disparities are also seen in syphilis – primary and secondary syphilis rates are disproportionately high among Black men: 27.9 in 100,000 compared to 5.4 in 100,000 for White men, although increases among White and Hispanic men have also been noted over the past several years [4]. Additionally, geographic disparities in syphilis prevalence have been documented. The Southeastern United States has the largest proportion of syphilis cases with 41% of cases reported there, although the West has the highest case rate (7.9 cases per 100,000) [10].

Among adolescents and young adults, the incidence of syphilis continues to increase. Between 2014 and 2015, primary and secondary syphilis among young people aged 15–19 increased 10.2%, and among those aged 20–24, rates increased 14.9%. Incidence rates were relatively lower among young women compared to young men (2.8 cases per 100,000 for 15–19-year-old women and 5.1 cases per 100,000 for 20–24-year-old women compared to 8 per 100,000 for 15–19-year-old men and 35.7 per 100,000 for 20–24-year-old men), but the incidence has increased in every sex and age category since 2013 [11]. Thus, while young, Black MSM have the highest risk of acquiring syphilis, it is important to keep in mind that rates have increased in adolescents and young adults of every age, gender, and sexual orientation.

Microbiology and Pathophysiology

Syphilis is a systemic infection with the spirochete *Treponema pallidum*, subspecies *pallidum*. Venereal syphilis infection occurs after the spirochete directly penetrates the mucous membranes or enters through the breaches in the skin that result from sexual contact. The first step of infection involves the spirochete attaching to the host cells and extracellular matrix, as it is primarily an extracellular pathogen. The spirochete then multiplies locally and disseminates via the lymphatic system and the bloodstream within minutes of infection. Because the spirochete is long and flat, it can easily penetrate human tissue and vascular structures via an undulating, corkscrew movement. This early and widespread hematogenous dissemination explains the eventual widespread involvement of the disease. The outer membrane of the spirochete lacks both lipopolysaccharide and toll-like receptor 2 (the latter of which can be found beneath the pathogen's outer membrane); this helps the spirochete to evade detection by the innate immune system and help to explain the lack of

systemic inflammation in primary syphilis [12]. Once opsonization occurs, spirochetes are more easily located and destroyed, causing a systemic inflammatory response and tissue damage that leads to the wide variety of clinical manifestations of secondary syphilis. *T. pallidum* does not appear to secrete any commonly recognized virulence factors. Despite the development of opsonic antibodies, the infection is not usually cleared, and the infection (if untreated) proceeds to the latent stages of the disease. Several mechanisms have been proposed to explain how *T. pallidum* evades the immune system, but the process is incompletely understood. It is clear, however, that *T. pallidum* is able to penetrate the central nervous system, the eye, and the placenta, all of which are considered "immune-privileged" areas where the infection can occur. Additionally, the spirochete's slow metabolism might work to its advantage, allowing it to slowly replicate even in non-"privileged" sites and still remain under the radar of the host's immune defenses. The factors that induce *T. pallidum* to begin dividing rapidly once again in some hosts (causing the manifestations of late syphilis) remain uncharacterized [13].

Clinical Manifestations

Syphilis is a chronic infection characterized by three stages of active disease, primary, secondary, and latent. However, syphilis can be asymptomatic, and unobtrusive lesions may go unnoticed; thus, not all patients are aware of having experienced each stage of the disease. The disease can be sexually transmitted only during the primary, secondary, and early latent stages, although vertical transmission can occur during any stage, including latency [14].

Primary syphilis is heralded by a *chancre* – a painless, indurated, clean-based ulcer – after 2–6 weeks of incubation following direct contact with another person's infectious lesion. Chancres are most often seen in men at the head of the penis, but can erupt anywhere that direct contact occurred. Chancres have been reported in the vagina, cervix, in and around the rectum, in the mouth, and even on the fingers and neck. The chancre usually heals spontaneously without scarring within 4–6 weeks, although with treatment it will likely regress more quickly (within 2–3 days). Regional lymphadenopathy may or may not be present and may or may not be tender [14].

Around 6–8 weeks after the healing of the chancre, secondary syphilis usually develops. The findings in secondary syphilis include generalized lymphadenopathy, a non-pruritic, maculopapular rash that often involves the palms and soles. However, the rash of secondary syphilis can be highly variable. The rash can be localized or widespread and can manifest as pustular or scaly in appearance (as opposed to the classic maculopapular description). In intertriginous areas (particularly the anogenital region), these lesions can coalesce to from *condylomata lata*, plaques resembling flat warts. Gray *mucus patches* may also be found on the oral or genital mucosa. All of these lesions are highly infectious through contact. Flu-like symptoms, such as sore throat, fever, and myalgias, are common. Other end-organ

manifestations, including hepatosplenomegaly, hepatitis, nephrotic syndrome, aseptic meningitis, uveitis, and generalized lymphadenopathy, have also been described [12].

If untreated, syphilis can progress to a latent stage. There are no clinical manifestations during this stage, and the disease can only be detected via serologic testing. The latent stage is then subdivided into early, late, and unknown latency. Early latent syphilis occurs within a year of infection – if the date of infection is over a year ago or unknown, the patient is treated as having late latent syphilis. About one-quarter of those in early latency will have a recurrence of secondary syphilis symptoms, usually within the first year [14].

After a variable period of latency, the disease may progress in about one-third of those infected to late manifestations of syphilis such as cardiovascular syphilis, gummas, or tabes dorsalis. Cardiovascular syphilis classically involves the ascending aorta and can cause aneurysms with or without aortic valve insufficiency and coronary artery stenosis. *Gummas* are granulomatous lesions that can occur anywhere on the body and may include cerebral locations with mass effect or local inflammation. Both cardiac manifestations and gummas have become very rare with the advent of effective antibiotic therapy, and given the long period of latency that usually precedes them, they would be particularly unlikely in adolescent patient population [14].

Neurosyphilis can occur at any time during the course of the infection. *T. pallidum* can be detected in the cerebrospinal fluid (CSF) early in the course of the disease even without symptoms [15]. Other manifestations of neurological involvement can include uveitis and cranial nerve palsies. Syphilis can also cause an aseptic meningitis or meningovascular syphilis, a type of inflammatory arteritis that can cause headaches, movement disorders, and behavioral changes, and even strokes and seizures later on. During late syphilis, general paresis or *tabes dorsalis* can occur. General paresis can cause progressive dementia, seizures, psychosis and other psychiatric manifestations. Tabes dorsalis, which involves damage to the posterior column of the spinal cord, presents as ataxia from loss of proprioception and sharp, radicular pain. The signs of tabes dorsalis include the Argyll Robertson pupil (pupil accommodates but does not react to light), loss of vibratory sensation, and loss of reflexes [14].

Ocular syphilis is another serious manifestation of syphilis that can occur either in the presence or absence of other nervous system involvement [15]. Symptoms may include eye redness and blurry vision that can progress to vision loss. Retinitis, optic neuritis, and retinal detachment can also be seen.

Diagnostic Testing

T. pallidum cannot be cultured. Diagnostic testing therefore relies on either direct detection using dark-field microscopy or tests to detect *T pallidum* from lesion exudate. Dark-field microscopy is a technically difficult test and therefore is rarely

performed. A presumptive diagnosis of syphilis is made with a combination of serologic tests used for screening and confirmatory testing.

Serologic tests can be divided into treponemal and non-treponemal tests. The non-treponemal tests, such as the rapid plasma reagin (RPR) and Venereal Disease Research Laboratory (VDRL) tests, are usually used for screening purposes. The non-treponemal tests detect the presence of an immune system product that is produced in response to an infection with *T. pallidum* (a non-specific cardiolipin-cholesterol-lecithin reagin antigen). False positives are a concern and are more likely in the setting of autoimmune disease, viral infections, pregnancy, intravenous drug use, advanced malignancy, tuberculosis, malaria, and rickettsial diseases. Persons with a reactive non-treponemal test should receive a treponemal test for confirmation [16].

The treponemal tests detect antibodies to *T. pallidum*. There are several treponemal IgG tests commercially available, and some of these tests can also detect false-positive treponemal tests that can occur but a false-positive reaction to both treponemal and non-treponemal tests is uncommon. The serologic diagnosis of syphilis relies on the combination of a reactive non-treponemal test and treponemal test [17].

In the usual sequence of syphilis serologic testing, a non-treponemal test (RPR or VDRL) is performed followed by a treponemal test. However, some clinical laboratories use a reverse sequence algorithm, or screening with a treponemal test followed by a non-treponemal test. If the treponemal test is positive, but the non-treponemal test is negative, a second treponemal test is then recommended. If the second treponemal test is positive but the patient has a past history of treated syphilis, then no treatment is required, unless there is a concern for re-exposure. If a patient was previously unaware of any history of syphilis, then the patient should be treated for late latent syphilis. The use of this reverse sequence algorithm may be more likely to diagnose early primary, previously treated, or long-standing untreated syphilis, all of which can be associated with a negative RPR (Fig. 11.3) [18].

Treatment

Syphilis is treated with parenteral penicillin G, regardless of the stage of the infection. Despite the fact that penicillin has been used to treat syphilis for more than 60 years, there has never been a documented case of penicillin resistance [5]. In very typical cases, treatment should be initiated based on clinical suspicion alone before laboratory results are available, because early treatment of syphilis helps to prevent further transmission [19].

For primary, secondary, or early latent syphilis, a single dose of 2.4 million units IM is given. Alternatives to penicillin include doxycycline (100 mg PO twice daily for 2 weeks) and ceftriaxone (1–2 g parenterally daily for 10–15 days), although data are limited on the optimal dose and duration of ceftriaxone. Azithromycin has documented efficacy against early syphilis; however, due to concerns about underlying resistance, it is not a recommended treatment option [5].

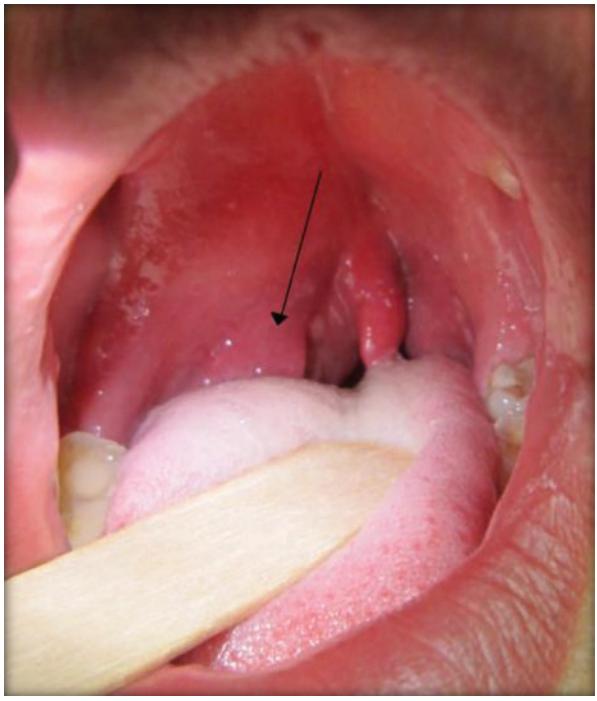


Fig. 11.3 Syphilis diagnostic testing algorithms

Late latent syphilis or syphilis of unknown duration is treated with 2.4 million units of benzathine penicillin G IM once a week for 3 weeks [18]. Again, doxycycline and ceftriaxone may be used as alternatives, although the optimal dose and duration of ceftriaxone are not known [5]. There is pharmacologic evidence to guide clinicians if a patient misses a dose, but clinical experience suggests that an interval of 10–14 days between doses may be acceptable [20].

After treatment, patients should receive follow-up non-treponemal testing and clinical evaluation at 6 and 12 months after treatment of early syphilis, as these tests reflect disease activity. Based on serologic testing, a fourfold decrease in the titer at 6–12 months after treatment is considered an appropriate decline. Those patients whose titers do not decrease fourfold may have treatment failure or a titer that is serofast. Further clinical evaluation and a CSF evaluation may be required [20].

In some cases, titers of non-treponemal antibodies decline, but the test never reverts to nonreactive. The serofast state may be explained by variability of host antibody response to infection, persistent low-level infection, and a false-positive non-treponemal test. After treatment of early syphilis, approximately 15–41% can remain in a serofast state after treatment. Re-treatment does not appear to benefit these individuals if there is no evidence of reinfection [5].

In patients with tertiary syphilis, a CSF analysis is warranted to evaluate for neurological involvement. If the CSF testing is negative for syphilis, then treatment for late latent syphilis – 2.4 million units of penicillin G IM once a week for

3 weeks – is recommended [17]. These patients should also be tested for HIV infection [20].

In the case of neurological, ophthalmologic, or audiologic symptoms during any stage of syphilis, lumbar puncture is required to evaluate for central nervous system involvement. Involvement of the central nervous system which includes ocular and auditory symptoms warrants intravenous penicillin because benzathine penicillin cannot reach sufficient concentration in the CSF. Intravenous aqueous crystalline penicillin G is used, 18 million to 24 million units per day in continuous infusion or divided into 6 daily doses for 10 to 14 days.

The Jarisch-Herxheimer reaction is an acute reaction that sometimes occurs following treatment of syphilis. It can occur with any antimicrobial but is most common after penicillin. It can occur in 10 to 35% of patients treated for syphilis [5]. Its symptoms, which usually occur within the first 24 hours of treatment, include fever, myalgias, and headache. Because the spirochete burden is highest in early syphilis, and the reaction is caused by the release of inflammatory factors from the killed organisms, the reaction most commonly occurs at that stage. Symptomatic treatment may be needed to support the patient through this brief but uncomfortable reaction [18].

Sexual partners of patients diagnosed with primary, secondary, and early latent syphilis should be treated for syphilis as well, regardless of their test results, if they had intercourse with the patient in the 90 days prior to diagnosis. If the intercourse occurred more than 90 days prior to diagnosis, treatment should be based on the results on serologic testing. The sexual partners of those patients with late latent and tertiary syphilis only require serologic testing if they are long-term partners of the patient, because the infection is not usually transmitted sexually during those stages. Those sexual partners should then be treated based on their test results. If the titers are high and the patient and sexual partner belong to a high-risk population, the sexual partner should be treated presumptively for early syphilis [18].

Prevention

Prevention of syphilis follows similar guidelines as those established for other sexually transmitted infections. Strategies include as screening of high-risk individuals and immediate treatment of the individuals and their partners. Additionally, the role of the health department in controlling syphilis outbreaks via mandatory notification programs should be emphasized. Barrier contraception (e.g., condoms) is also a useful prevention strategy.

Screening and treating are effective forms of prevention in high-risk populations. The United States Preventive Services Task Force (USPFTF) updated their screening recommendations for syphilis in asymptomatic, nonpregnant adults in 2016. Syphilis screening is recommended in high-risk populations, such as MSM and persons living with HIV, and should be screened periodically (Grade

A recommendation). Additional risk factors to consider include a history of incarceration, commercial sex work, geography (metropolitan centers in the Southeastern and Western United States), race/ethnicity, and being a male younger than 29 years. However, the optimal interval for screening has not been well established. Initial studies do suggest that detection increases when the interval is increased to 3 months from once a year in high-risk individuals [10]. Similarly, the CDC recommends at least annual screening in sexually active MSM and persons living with HIV, with more frequent screening depending on ongoing risk behavior. Screening for syphilis should also be considered in correctional facilities based on local epidemiology and institutional prevalence [20].

The USPSTF and the CDC have several further recommendations for syphilis prevention. First, high-intensity behavioral counseling for all sexually active adolescents to prevent sexually transmitted infections is recommended [19]. The USPSTF also notes that, in the case of syphilis prevention, the role of local health departments and public health agencies is critical. Investigating incident cases and finding and treating partners are imperative in controlling the spread of syphilis. Primary care providers should also be aware of local laws regarding reporting to public health officials [10].

Condoms are only effective at preventing transmission of syphilis if the condom covers the chancre. Promotion of condom use is still helpful to decrease syphilis rates, however, as currently only 56.9% of teenagers report that they used a condom during their last episode of sexual intercourse [21]. Like other ulcerative sexually transmitted infections, syphilis can be transmitted via oral and digital sex. In fact, one observational study in MSM found that 13.7% of syphilis cases were contracted via oral sex [21]. Thus, condoms, dental dams, female condoms, and other barrier forms of STI prevention should be encouraged.

Unfortunately, there is no vaccine for syphilis. A vaccine using irradiated *T. pallidum* has been shown to provide protection from infection in animal models. Recent articles have suggested that syphilis would be a prime candidate for further vaccine research, but no vaccine has made it to human trials [22].

Other Considerations

HIV Coinfection

Syphilis and HIV are closely interrelated and have been so since the beginning of the AIDS epidemic. Worldwide, 9.5% of people living with HIV are reported to have syphilis [23]. Ever since the early 1990s, syphilis has been considered a risk factor for HIV infection both because of facilitated transmission [24] and overlapping risk factors and behaviors [25]. For these reasons, persons living with HIV should be screened for syphilis at least annually as part of their routine care, although more frequent screening can be performed based on the assessment of risk behaviors [20].

Syphilis is often associated with high-risk sexual behavior and HIV coinfection. HIV coinfection has been reported as high as 50–70% among MSM diagnosed with primary or secondary syphilis [5]. In individuals living with HIV, the presentation of syphilis is highly variable. Primary and secondary stages of syphilis may overlap, and the cutaneous manifestations may range from impressive to relatively asymptomatic [26].

Data from before the 1980s and 1990s (prior to the advent of highly active combination HIV therapies) suggests that HIV coinfection presents an increased risk for progression to neurosyphilis with a shorter latency period. However, effective treatment of HIV appears to reduce this risk. Subsequent serologic testing should occur more frequently in people with HIV (e.g., at 3, 6, 9, 12, and 24 months) [5].

Finally, if the individual with HIV is severely immunocompromised, initiation of treatment of the HIV with antiretrovirals can result in immune reconstitution syndrome in those persons with undiagnosed syphilis; however, this is uncommon [26].

Pregnancy

Recent reports indicate an increase in syphilis in women in the United States and globally [27]. In utero transmission of syphilis can have effects in the developing fetus that range from silent to severe consequences. Fetal loss and stillbirth occur more frequently in infected mothers. However, two-thirds of infants with maternally acquired syphilis are asymptomatic at birth. Symptoms most commonly appear during the first 3 months of life, including rash, hepatosplenomegaly, neurosyphilis, pneumonitis, failure to thrive, blood-tinged nasal discharge, meningitis, and pseudoparalysis due to long bone damage. Late congenital syphilis, in which symptoms appear after the age of two, involves gummas on the nasal septum, hard palate, as well as the skull and tibias, resulting in saber shins. Teeth and jaw bone deformities lead to Hutchinson incisors, mulberry molars, rhagades, and bulldog facies. Tabes dorsalis and other manifestations of neurosyphilis may occur even into adolescence. Blindness due to interstitial keratitis and sensorineural deafness may also occur [27]. Because of these significant ramifications, it is of vital importance to treat syphilis immediately during pregnancy.

Primary and secondary syphilis carry the highest risk for vertical transmission, but even with late latent syphilis and low titers, the risk of transmission is still significant. The only recommended treatment during pregnancy is penicillin G, so women with penicillin allergy should undergo desensitization. Some evidence suggests that additional therapy can be beneficial in the case of pregnancy, so in early syphilis, a second dose can be given 1 week after the first. Missed doses are unacceptable given the severe consequences of vertical transmission, and so treatment should be reinitiated from the beginning of the series following any missed dose. Follow-up testing should occur at 28–32 weeks, as well as at delivery [19]. Despite the risk of the Jarisch-Herxheimer reaction provoking early labor or fetal distress,

treatment should not be delayed or withheld because of the potential for this reaction causing harm to the developing fetus [5].

MSM

The increase in syphilis among MSM has been attributed to several different factors, including a decrease in safer sex practices, changing harm reduction/HIV prevention strategies, the increased use of online social networks to find sexual partners, decreasing mortality due to HIV, and decreased funding for STI prevention [6]. The decline in safer sex practices particularly among MSM has been ascribed to HIV prevention fatigue, optimism regarding HIV treatment, and an increase in recreational drug use among MSM, particularly methamphetamines. Harm reduction strategies like serosorting (choosing sex partners based on HIV status in order to have unprotected sex) and pre-exposure prophylaxis (PrEP) are somewhat effective against preventing HIV but do not decrease transmission of other STIs like syphilis [7]. Online social networks and dating apps have increased the pool of sex partners and may facilitate anonymous sex [8], which in turn makes it more difficult to treat sexual partners once syphilis is diagnosed. Additionally, because of overlapping risk factors, the decrease in mortality due to HIV has increased the size of the population at risk for syphilis [9]. Finally, funding for STI prevention has not kept pace with the increasing incidence. States have experienced budget cuts for STI prevention services, and HIV, while an important cause, has decreased spending in other STI prevention efforts [6]. All of these factors combined have contributed to the resurgence of syphilis in the United States [2].

Although general screening for syphilis in asymptomatic individuals is not recommended, the CDC does recommend that young MSM be screened for syphilis at least annually. Increased syphilis screening practices have demonstrated a doubling of the detection of early syphilis, although the majority of syphilis diagnoses are in patients who sought care for symptoms. Screening is especially important because primary syphilis, like all ulcerative sexually transmitted infections, facilitates HIV infection [20].

WSW

Men who have sex with men are certainly at the highest risk for syphilis infection, but other transmission between women who have sex with women (WSW) has been reported, likely through oral sex [20]. As noted above, rates are relatively low but still increasing among young women [11], so providers should emphasize that risk still exists for WSW (as well as heterosexual women).

Case Conclusion

The patient's RPR was reactive at 1:32 and a treponemal IgG was positive. These serologic tests in combination with his clinical presentation is consistent with secondary syphilis. Intramuscular benzathine penicillin (2.4 million units) was administered per national guideline recommendations. His symptoms began to resolve after the penicillin injection, and after 2 days, he was afebrile with resolving odynophagia and rash. When he returned to clinic 8 days later, his lymphadenopathy and tonsillitis had completely resolved.

Despite having well-described, classic symptoms, syphilis was coined "the great imitator" by Sir William Osler for its ability to manifest in unexpected ways. A handful of case reports of syphilis presenting as tonsillitis have been reported in the literature. Cases of syphilitic tonsillitis have been associated with both secondary and late syphilis. Both bilateral and unilateral tonsillitis have been described. In particular, syphilitic tonsillitis appears to be unusually common in the HIV+ MSM population.

Syphilis is highly contagious but it is also easily treated. Avoidance of late complications of syphilis is dependent on its early detection. Syphilis screening should be performed regularly in all high-risk populations, including sexually active adolescents and young adults, and particularly young MSM.

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Chapter 12
Gonorrhea in Adolescents and Young Adults

Valeria D. Cantos and Carlos del Rio

Case Study
A 21-year-old man presents to his primary care physician with dysuria and purulent urethral discharge for 2 days. He reports having condomless insertive anal sex with a new male partner 5 days prior to the onset of symptoms. On physical examination, he is anxious but otherwise in no acute distress. During his genital examination, a moderate amount of mucopurulent discharge is expressed from his meatus.

Questions for Consideration
- What is your differential diagnosis?
- Which diagnostic tests would you order at this point?
- How would you treat this patient?

Epidemiology

In 2015, 395,216 cases of gonorrhea were reported in the USA for a rate of 123.9 cases per 100,000 population [1]. Gonorrhea represents the second most common notifiable disease in the US. The national rates of reported gonorrhea infection in the USA have been steadily increasing since 2009, when they were at a historic low of 98.1 cases per 100,000 population. Regional disparities are seen as well; the South has the highest rates (146.3 cases per 100,000 population) followed by the West (118.0 cases per 100,000 population).

It is estimated that 70% of all gonococcal infections occur in people aged 15–24 years [2]. Among them, only 35% of infections are diagnosed and reported

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to the CDC [2]. In 2014, men and women aged 20–24 years had the highest rate of gonorrhea compared to other age groups [1]. Women aged 15–19 years had the second highest rate of gonorrhea among other women in the US: 430.5 cases per 100,000 females compared to the national rate of 110.7 per 100,000 population [3].

There are unique factors that render youth more vulnerable to STIs in general, including gonorrhea. In terms of anatomy, the cervix histology of younger females is different than the one from older women. Adolescents have a predominance of columnar epithelial cells, which are more susceptible to infection by GC and CT than squamous epithelial cells, which are often found in older women [4]. Additionally, youth, especially young MSM, tend to have large and high-density sexual networks that facilitate STI transmission [5]. Finally, adolescents, particularly African American youth and those from low socioeconomic status (SES), are more likely to be uninsured and to have limited transportation compared to adults, and both represent barriers to their access to healthcare [6].

Microbiology

Neisseria gonorrhoeae, also known as gonococcus (GC), is a gram-negative, oxidase-positive round bacteria (coccus) that usually grows in pairs (diplococci) [7]. It is differentiated from other *Neisseria* species such as *N. meningitidis* and nonpathogenic *Neisseria* by its ability to produce acid from glucose (but not from maltose, sucrose, fructose, or lactose) [7]. In order to successfully grow in the laboratory, it requires a specific temperature (35–38 °C), a moist atmosphere enriched with CO_2 (3–7%), and a blood-enriched agar such as chocolate agar. Specimens obtained from non-sterile sites should be inoculated in selective agar containing antibiotics that inhibit the growth of commensal bacteria and fungi such as the modified Thayer-Martin agar [7]. Plates should not be incubated for longer than 48 hours because autolysis may occur with prolonged incubation.

GC has multiple structures on its surface to facilitate mucosal attachment and to evade the human's immune system. Some of these virulence-enhancing structures are summarized in Table 12.1.

Pathophysiology

N. gonorrhoeae is an exclusive human pathogen. Mucous membranes of the genital tract, oropharynx, rectum, and eye constitute the main ports of entry and targets of infection [8]. The surface components of the bacteria play a fundamental role in the pathogenesis of disease in both men and women. However, infection of the genitourinary tract manifests itself differently in males than in females [9]. While men usually present with acute symptomatic urethritis, women with gonococcal infection can be asymptomatic in 40–90% of cases [10–12].

Table 12.1 *Neisseria gonorrhoeae* surface structures and their functions

	Description/function
Pili	Hairlike structures attached to the bacterial surface Host cell attachment Resistance for phagocytosis High antigenic variability
Porin (Por)	Surface pores Phagocytosis inhibition Nutrient supply
Lipooligosaccharide (LOS)	Endotoxic effect Evasion of immune recognition
Opacity proteins (Opa)	Colony adhesion Attachment to host cells Interaction with PMNs

In the male urethra, pili facilitate the initial attachment of GC to the urethral epithelial cells; lipooligosaccharides (LOS) create a closer interaction between them and trigger the release of pro-inflammatory cytokines including IL-6, IL-8, and TNF-α which leads to mucosal infiltration by neutrophils [13]; opacity proteins are involved in the intracellular invasion of epithelial cells [14, 15]. Once within the cell, bacteria incorporate sialic acid to their LOS rendering them resistant to the bactericidal effect of human serum, which may allow them to disseminate hematogenously in rare cases [16]. Finally, infected cells shed into the urethral lumen and along with neutrophils cause the characteristic purulent meatal exudate.

In females, it has been postulated that certain hormone-induced properties of the cervical epithelial cells and the cervical mucus favor GC's abilities to inactivate complement activity and the cell signal transduction cascades, inhibiting the inflammatory response which would explain the low levels of pro-inflammatory cytokines found in the supernatant of cervical epithelial cells of women with documented gonococcal cervicitis and the higher rates of asymptomatic infection when compared to males [9]. Ascendant infection of the endometrium constitutes a pivotal step between the mostly asymptomatic lower genital tract infection and the symptomatic infection of the fallopian tubes, characterized by severe inflammation and scarring [17]. GC infects nonciliated cells but exerts its cytotoxic effects on ciliary cells, causing its shedding into the tubal lumen [9]. The loss of ciliary cells impairs ovum transportation to the endometrium, causing ectopic pregnancy or infertility [18]. Moreover, inflammation in the fallopian tubes triggers fibrosis and adhesion formation which can lead to lumen obstruction [18].

GC are extremely susceptible to the bactericidal activity of serum and are killed rapidly by the complement membrane attack complex. The classical pathway of complement is the primary mechanism of complement-mediated killing of GC, and the ability of GC of a particular isotype to inactivate the classical pathway confers significant survival advantage to the organism. Individuals who have terminal complement deficiencies (C5, C6, C7, C8, and/or C9) are unable to form the membrane attack complex and thus are at increased risk for invasive *Neisseria* infections [9].

Clinical Presentation

General Considerations

When evaluating a patient who presents to the clinic with concerns of having a sexually transmitted infection (STI) or for STI screening, it is important to address questions regarding sexual practices including history of sex with partners who have STI symptoms or who have been recently diagnosed with an STI, as well as the type of sexual practices, including receptive or insertive oral, vaginal, and anal sex [19]. Such information will guide clinicians to evaluate for multiple sites of involvement during the physical exam and to obtain samples of such sites for testing (pharyngeal, genital, rectal). (*See* Chap. 2: "*Approach to the Sexual History and Physical Exam*" *for further detail*.)

Given the differences in the clinical presentation of genitourinary infections in men and in women, we will describe them separately. We will then present the signs and symptoms of gonococcal infection in other mucosal sites, and finally, we will address disseminated gonococcal infection (DGI).

Genitourinary Infection in Men

Acute urethritis is the most common presentation in males [10]. It is estimated that the incubation period for GC urethritis ranges from 3 to 5 days [20]. Mucopurulent urethral discharge with associated dysuria is frequently observed in cases of GC urethritis in men, although it can also present as dysuria without discharge [21]. Asymptomatic urethral infection can be seen in less than 10% of confirmed cases of gonorrhea in men [22]. Sometimes, infection can ascend to the epididymis and/or the testicles (epididymitis or epididymo-orchitis) causing acute posterior testicular pain, usually unilateral and alleviated by elevating the scrotum, as well as scrotal swelling or erythema [23].

Genitourinary Infection in Women

Women with confirmed GC genitourinary infection are often asymptomatic [22]. When present, symptoms may include dysuria, vaginal discharge, intermenstrual or postcoital bleeding, and lower abdominal pain [19]. Most of these symptoms are the consequence of inflammation of the uterine cervix (cervicitis). In order to diagnose it, visualization of the cervix via speculum examination is required. Easily induced endocervical bleeding ("friability") and mucoid, mucopurulent, or purulent endocervical discharge have high positive predictive values for cervicitis [24].

Acute salpingitis or acute pelvic inflammatory disease (PID) occurs in some cases after infection ascends from the cervix, through the endometrium, to the fallopian tubes. GC can be found in the cervix of 20–80% of women with acute salpingitis [25]. The classical presentation of acute PID is acute-onset lower abdominal pain shortly after the onset of menses [26] along with the previously listed symptoms of cervicitis and sometimes fever, nausea, and vomiting [27]. The typical signs of PID during physical examination include cervical motion tenderness and uterine and adnexal tenderness. Per the CDC guidelines, the presence of unexplained lower abdominal pain in a young female along with one of the abovementioned physical exam findings should prompt physicians to start empiric treatment for PID and to perform additional testing including microscopic examination of the vaginal fluid looking for white blood cells (WBC) along with GC and chlamydia NAAT in endocervical or vaginal fluid [28].

Subclinical PID – having histopathological signs of PID in the absence of symptoms – has been found in 26% of women with gonococcal cervical infection [29]. Hence, many cases of PID go unrecognized, and persistent inflammation eventually can lead to fibrosis and scarring of the fallopian tubes. Sixteen percent of women with acute PID will go on to develop infertility [30], one-third of them could experience chronic pelvic pain [31], and 0.6–9% will have an ectopic pregnancy [32]. Screening for and treating acute gonococcal infections has proven to be an effective strategy in decreasing the rates of the abovementioned long-term sequelae [33].

Anorectal Infection

Among individuals who engage in receptive anal intercourse, men have a higher risk of acquiring anorectal GC than women [34]. Infection is usually asymptomatic, but approximately 20% of patients can present with anal pruritus or pain, mucopurulent or bloody rectal discharge, tenesmus, and sometimes constipation [19, 21, 34].

Pharyngitis

Patients with gonococcal pharyngitis usually acquire the infection via the oral-genital route. Less than 20% of individuals with a positive pharyngeal culture for GC are symptomatic [35]. If present, the most common symptoms are sore throat and fever [19, 21]. On physical exam, the oropharynx can be erythematous and have mucopurulent exudates along with tender cervical lymphadenopathy [19].

Conjunctivitis

Gonococcal conjunctivitis is mostly a disease of newborn infants. In the US, 28% of newborns born from a mother with gonococcal disease will develop gonococcal ophthalmia neonatorum [36]. The United States Preventive Services Task Force (USPSTF) recommends universal GC prophylaxis for all newborns using an ocular topical medication such as erythromycin within 24 hours of birth (grade A recommendation) [36].

Autoinoculation (spread of the infection from the anogenital region to the eyes through the hands of the same individual) is the most common route of infection of adolescent/adult gonococcal conjunctivitis [37]. It typically presents with severe conjunctival injection and abundant mucopurulent discharge and is often accompanied by palpebral edema and preauricular lymphadenopathy [38]. If left untreated, complications include uveitis, keratitis, and even corneal perforation [39].

Disseminated Gonococcal Infection

Disseminated gonococcal infection (DGI) presents in 1–3% of patients with mucosal gonococcal disease [40]. It occurs as a consequence of GC entering the bloodstream (gonococcal bacteremia) and classically presents with either the dermatitis/polyarthritis syndrome or frank septic arthritis [7]. The female to male ratio for DGI is 4:1 and affects women especially during pregnancy or the perimenstrual period [41]. It has been postulated that the change in the colonial phenotype of GC during menses or during pregnancy, from an opaque to a transparent colony type that is more invasive, might favor bacteremia and hence lead to disseminated disease [41]. As stated above, patients with terminal complement deficiency are at high risk of DGI. The dermatitis/polyarthritis syndrome is characterized by fever, a maculopapular or pustular rash, and migratory polyarthralgias, due to either tenosynovitis or arthritis [42]. True septic gonococcal arthritis presents in less than 50% of cases of DGI. It is usually monoarticular (knees, wrists, ankles) and presents with typical signs and symptoms of acute synovitis: warmth, edema, erythema, and severe limitation in active and passive range of motion of the affected joint [43]. Unusual presentations of DGI include infective endocarditis and meningitis. Gonococcal endocarditis occurs in 1–2% of patients with DGI, and it is usually diagnosed after approximately 6 weeks from the onset of symptoms [44]. The aortic valve is more commonly affected and vegetations are usually large. More than half of the patients with GC endocarditis will require valve replacement, and the mortality can be as high as 19% in spite of medical and surgical treatment [44]. Gonococcal meningitis was first reported in 1922, and since then, approximately 30 cases have been described in the literature [40]. Based on the survival rate of cases of GC meningitis in the pre-antibiotic area, some postulate that GC meningitis might be a milder

entity than other bacteria that cause meningitis (such as *N. meningitidis* or *Streptococcus pneumonia*) [45].

Diagnosis

There are several diagnostic tests that can be done to identify GC. The sensitivity and specificity of each one of them can vary depending on the clinical presentation of the infection (asymptomatic vs. symptomatic) and the infection site (mucosal vs. disseminated), and there are differences even within the various types of mucosa involved (pharyngeal vs. genital vs. rectal). Regardless of which method is used, all patients diagnosed with gonorrhea should also be tested for other STIs including *Chlamydia trachomatis* (CT), syphilis, and HIV.

Gram Stain Microscopy

Compared to culture, the presence of oxidase-positive gram-negative diplococci within neutrophils in a urethral smear has a sensitivity of 80% and a specificity of 95% in men with urethritis [46]. In symptomatic women, the sensitivity and specificity of the cervical gram stain are 70% and 97%, respectively [47]. In asymptomatic patients or in other mucosal sites including the pharynx, the synovium, or the rectum, the sensitivity and specificity are much lower, and gram stain is therefore not recommended to test for GC infection in these sites [48]. Moreover, *N. meningitidis* and nonpathogenic *Neisseria* are also gram-negative diplococci that need to be differentiated from GC by culture and biochemical testing.

Culture

Before the advent of nucleic acid amplification testing (NAAT), culture was the gold standard to diagnose gonorrhea. In order to isolate GC, samples obtained from non-sterile sites such as an endocervical or a urethral swab need to be plated in a selective (antibiotic-containing) agar, such as the modified Thayer-Martin media, that inhibits the growth of nonpathogenic *Neisseria* and other commensal organisms [49]. In this setting, the sensitivity of GC culture is more than 95% for symptomatic males and between 50 and 80% for women [7, 50]. If samples are obtained from sterile sites such as the synovium or the bloodstream, a nutrient-rich, nonselective agar (e.g., chocolate agar) should be used [51].

Culture has some disadvantages. First, the use of different transport media, time to plating, and even media temperature can affect its positive yield [52]. Second, in

cases of DGI, only 50% of synovial and blood cultures will be positive, while 80% of the cultures obtained from the genital tract will be positive [43]. Third, this technique is time-consuming and requires at least 48 hours before a diagnosis can be made.

In spite of these limitations, culture offers the advantage of having a live organism in which antibiotic susceptibility testing can be performed, especially in cases of treatment failure [51]. In case multiple samples are to be obtained for testing, it is recommended that the sample for culture should be collected first, to increase its positive yield [51].

Nucleic Acid Amplification Tests (NAATs)

There are currently three types of NAATs available for detection of GC based on the technology used to amplify nucleic acids: polymerase chain reaction (PCR), strand displacement amplification (SDA), and transcription-mediated amplification (TMA) [51]. All of them test concomitantly for CT and have been approved by the US Food and Drug Administration (FDA) to diagnose genital GC and CT infections [50, 51]. When compared to in vitro culture, NAATs of endocervical swabs are more sensitive (90% vs. 70%) and are close to 100% specific [50]. Moreover, self-collected vulvovaginal swabs have shown to have higher sensitivity than endocervical cultures (96% vs. 81%) and almost identical sensitivity compared to endocervical NAATs (99% vs. 96%) [53]. Lastly, sensitivity of urine NAATs in females with confirmed gonorrhea infection is lower (80%) than in men (93%) [54]. Based on this data, the CDC recommends NAATs for screening and diagnosis of GC for both symptomatic and asymptomatic individuals using self-collected vaginal swabs for women and first-catch urine for men [51].

Extragenital GC infections are common and often asymptomatic in MSM [55]. Although they are not technically FDA approved for extragenital testing, the CDC recommends using NAATs for testing pharyngeal and rectal samples in this population given their superiority in detecting GC when compared to culture [51, 56]. The sensitivity of TMA testing to detect GC in oropharyngeal samples in a study of over 1000 individuals who attended an STI clinic was 84%, compared to 72% for SDA and 41% for culture [56]. It is not recommended to use PCR technology on oropharyngeal samples since it can cross-react with other *Neisseria* species and hence has low specificity (79%) compared to TMA (99.6%) [56].

Treatment

Antimicrobial resistance of GC is a major public health problem in the USA and worldwide. In 1986, the Gonococcal Isolate Surveillance Project (GISP) was established by the CDC as a national surveillance program to monitor trends in antimicrobial susceptibilities of GC in 27 US sites [57]. Over time, *N. gonorrhoeae* has

acquired resistance to a multitude of antibiotics including penicillin, tetracycline, and ciprofloxacin. Additionally, GC has developed reduced susceptibility to drugs that were previously first-line such as cefixime, as evidenced by higher minimal inhibitory concentrations (MIC) – significantly limiting their use [57]. Modifications of treatment guidelines have ensued in an attempt to stop or at least decelerate this trend. In 2014, GISP reported an increase in the percentage of isolates with reduced azithromycin susceptibility ([MIC ≥2 μg/mL]) from 0.6% in 2013 to 2.5% and an increase in the percentage of isolates with reduced cefixime susceptibility ([MIC≥0.25 μg/mL]) from 0.4% in 2013 to 0.8% in 2014 [57]. These changes in susceptibilities occurred even after the latest modifications of the treatment recommendations took effect, namely, removing cefixime as a first-line treatment and using a ceftriaxone/second drug dual-therapy combination. These trends raise concern for potential emergent resistance to the only first-line regimen available to date (ceftriaxone/azithromycin). Table 12.2 summarizes the 2015 CDC treatment recommendations.

General Treatment Considerations

A ceftriaxone-based dual-therapy regimen is the recommended treatment strategy by the CDC STD Treatment Guidelines since it has sustained bactericidal activity [28]. The recommended second drug is azithromycin and not doxycycline given the risk of tetracycline-resistant GC, especially in isolates with reduced susceptibility to cefixime [28]. Patients should abstain from having sex until after 7 days of treatment, and all sexual partners within the past 2 months should be notified, tested, and treated if positive. All patients treated for urogenital gonorrhea should be retested in

Table 12.2 2015 CDC recommendations for the treatment of gonorrhea [28]

	First-line	Alternative	Notes
Uncomplicated urethritis/ cervicitis/ proctitis	Ceftriaxone 250 mg IM single dose + azithromycin 1 g PO single dose	1. Cefixime 400 mg PO single dose + azithromycin 1 g single dose 2. If severe cephalosporin allergy: gemifloxacin 240 mg PO single dose + azithromycin 2 g PO single dose	Cefixime should be used only when ceftriaxone is not available
Gonococcal pharyngitis	Ceftriaxone 250 mg IM single dose + azithromycin 1 g PO single dose	n/a	GC pharyngitis are more difficult to eradicate than genital and rectal infection
Gonococcal conjunctivitis	Ceftriaxone 250 mg IM single dose + azithromycin 1 g PO single dose	n/a	Consider infectious diseases consultation.

(continued)

Table 12.2 (continued)

	First-line	Alternative	Notes
PID Mild to moderate illness	Ceftriaxone 250 mg IM single dose + doxycycline 100 mg PO BID +/- metronidazole 500 mg PO BID for 14 days	Cefoxitin 2 g IM + probenecid 1 g PO single dose + doxycycline 100 mg PO BID +/- metronidazole 500 mg PO BID for 14 days	Criteria for hospitalization: pregnancy, TOA, severe disease: fever, nausea, vomiting, inability to tolerate oral medication, failure of oral regimen IV therapy can be stopped after 24–48 of clinical improvement For cefotetan or cefoxitin regimen: switch to PO doxycycline to complete 14 days of therapy For clindamycin/gent regimen: switch to PO clindamycin or PO doxycycline to complete 14 days of therapy
PID Severe illness	Cefotetan 2 g IV BID + doxycycline PO or IV every 12 hours for 14 days OR Cefoxitin 2 g IV every 6 hours + doxycycline PO or IV every 12 hours for 14 days	Clindamycin IV every 8 hours + gentamicin: loading dose 2 mg/kg IV or IM once, followed by maintenance dose 1.5 mg/kg every 8 hours. Daily dose of 3–5 mg/kg can also be used	
TOA	Same as severe PID	Same as severe PID	Inpatient observation recommended for at least 24 hours IV therapy can be stopped after 24–48 of clinical improvement Switch to PO doxycycline AND PO clindamycin to complete 14 days of therapy
DGI	Ceftriaxone 250 mg IM every 24 hours + azithromycin 1 g PO single dose	Cefotaxime 1 g IV every 8 hours OR Ceftizoxime 1 g IV every 8 hours + Azithromycin 1g PO single dose	Recommend infectious disease consultation Examination for endocarditis and meningitis required Antibiotic susceptibilities testing required Duration of treatment: not well established

Abbreviations: *PO* by mouth, *IM* intramuscular, *IV* intravenous, *PID* pelvic inflammatory disease, *TOA* tubo-ovarian abscess, *BID* twice a day, +/− with or without

3 months. In cases of pharyngeal gonorrhea, a test-of-cure is only recommended if the patient received an alternative regimen [28].

Treatment failure should be considered in patients who have abstained from sex since receiving treatment and who present with persistent symptoms within 3–5 days of treatment or who have a positive test-of-cure (culture or NAAT) after 7 days of treatment [28]. However, since reinfection is much more common than true treatment

failure, clinicians should retreat with the first-line regimen first (ceftriaxone/azithromycin) before using other drugs, in the abovementioned circumstances. Prior to retreating, new samples should be obtained and sent for antibiotic susceptibility testing to the CDC (telephone: 404-639-8659). Also, an infectious disease specialist and the local health department should be involved in cases of suspected treatment failure [28].

Prevention

In addition to condom use and safe sex practices, diagnosis and treatment of asymptomatic patients and their partners represents an important prevention strategy. The USPSTF recommends gonorrhea screening for all sexually active women age 24 and younger and for older women at increased risk of infection, namely, "new or multiple sex partners, a sex partner with concurrent partners, a sex partner with a STI, inconsistent condom use among persons who are not in mutually monogamous relationships, previous or concurrent STI; and exchanging sex for money or drugs." [58] There is currently no available data to guide specific screening frequency [58]. Additionally, the CDC recommends annual pharyngeal, urethral, anal, and rectal GC/CT screening in MSM. All females aged 35 and younger upon their entry to jail should also be screening for GC as well as high-risk pregnant women at their first prenatal visit and during the third trimester if the risk behaviors continue and if they tested positive during the first trimester screening [28]. For people living with HIV, screening for GC should be done in all sexually active individuals at the time of the first HIV evaluation and at least annually thereafter. In both MSM and persons infected with HIV, screening frequency should be increased to 3–6 months in high-risk cases [28].

It is estimated that 30–40% of adolescents in the USA do not get an annual health checkup [59]. School-based STI screening (SBSS) has been proposed as a feasible and cost-effective strategy to overcome this difficulty. It has been launched in five jurisdictions in the USA so far (NYC, Philadelphia, Michigan, rural Pennsylvania, and New Orleans) with good results in terms of number of students tested and increased rates of detection and treatment of GC and CT [6]. However, SBSS has not shown to help decreasing the prevalence of GC or CT or increasing youth's knowledge about STIs [6].

Case Conclusion

This patient is presenting with classical signs of acute mucopurulent urethritis. Gonorrhea and chlamydia trachomatis are on the differential. After obtaining a urine sample to be sent for GC/CT NAAT testing, this patient needs to be treated empirically with ceftriaxone 250 mg IM once and azithromycin 1 g by mouth (single dose). A repeat urine GC/CT NAAT should be ordered in 3 months.

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Chapter 13
Chlamydia

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Case Study

A 16-year-old male patient comes in to see his primary care doctor for an acute care visit. He has a chief complaint of a penile discharge and burning with urination. He also complains of mild fatigue but otherwise feels well. On further questioning, he is sexually active with multiple male partners and states he uses condoms approximately 10% of the time. His last anonymous sexual encounter was 3 weeks ago with a partner whom he met on a website. He also had sex with his regular partner last week, but his regular partner doesn't have any symptoms. He has never been tested for HIV or other sexually transmitted infections.

On physical examination, he is afebrile. His genitourinary exam is notable for a purulent penile discharge. He is also noted to have very mild diffuse lymphadenopathy in the inguinal areas.

His physician prescribes treatment and orders testing for a range of sexually transmitted infections, including HIV. He is counseled to abstain from sex for 7 days after treatment. A urine NAAT for chlamydia comes back positive. With treatment, the patient feels well and is no longer having symptoms.

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His partners in the last 60 days are tested and treated for exposure to chlamydia despite not having symptoms. His HIV test is negative, and given his risk factors, he is counseled on PrEP (pre-exposure prophylaxis) for HIV.

Questions for Consideration

- What are the clinical features of chlamydia infection?
- What treatment is indicated at this time?
- How should the patient be counseled to avoid further transmission?

Microbiology and Pathophysiology

Chlamydia are gram-negative obligate intracellular bacteria that rely on the host cell for all metabolic needs. They are exquisitely adapted to life inside cells and have specialized cell types for replication and cellular invasion. This developmental program alternates between two differentiated cell types, the elementary body (EB) and reticulate body (RB), and is critical to the completion of its life cycle [1]. The genus Chlamydia contains the causative agents of a number of important pathogens of humans. C. psittaci causes zoonotic infections resulting in pneumonia, while C. pneumoniae is a human pathogen that causes respiratory disease and is linked to atherosclerosis. Biovars of C. trachomatis are the causative agents of trachoma, the leading cause of preventable blindness worldwide, as well as the sexually transmitted disease Chlamydia. Irrespective of the resulting disease, all chlamydial species share the same obligate intracellular life cycle and biphasic developmental cycle.

The cell-type-specific division of labor (replication = RB, cell invasion = EB) in these pathogens generates a life cycle that results in a viral-like one-step growth curve with a defined eclipse period when no infectious progeny is present. Chlamydial pathogenesis is dependent on balancing the need to replicate with the need to create infectious progeny. The infectious cycle starts with the elementary body (EB) cell type binding to target cells and inducing uptake through engagement of a specialized secretion system called the type III secretion system (T3SS) and delivery of effector proteins directly into the target cell cytoplasm [2–4]. This pathogen-directed endocytosis results in the EB residing in a membrane-bound vesicle derived from the plasma membrane of the host cell and is termed the chlamydial inclusion. Chlamydia alters the properties of this vacuole shortly after entry by insertion of proteins into the inclusion membrane [5–8]. These membrane modifications ensure that the inclusion is not acidified by fusion with the endocytic or lysosomal pathway [9–11]. The diverse array of inclusion membrane (Inc) proteins give the inclusion unique properties and make the inclusion significantly different from other membrane systems of the host cell. One of these Inc proteins, IncA, confers homotypic fusion properties to the inclusion promoting fusion of nascent inclusions in multiply infected cells [12]. Additionally, the inclusions are trafficked to the microtubule-organizing center (MTOC) of the cell through hijacking the

dynein microtubule motor protein [13]. The inclusion remains associated with the MTOC throughout the rest of the developmental cycle through continued interaction with dynein and the minus ends of microtubules [13–15]. The mature inclusion has unusual biophysical properties; it has a characteristic spacious inflated morphology, is neutral in pH and has an ionic environment identical to the host cytosol, and is permeable to small ions [16]. To increase in size and acquire nutrients, the inclusion interacts closely with the exocytic compartment intercepting the lipids sphingomyelin and cholesterol from the Golgi [17–19]. In addition to intercepting lipids from the Golgi, the chlamydial inclusion closely associates with the host cell ER system to obtain other nutrients through this unique interaction [20].

Late in the developmental cycle, RBs undergo secondary differentiation asynchronously back to the infectious EB form as the inclusion becomes filled with RBs. This step is characterized by a condensation of the chromosome to form a densely packed nucleoid structure, leading to a reduction in the size of the cell from 1 to 0.3 μm in diameter. The outer membrane proteins of the EB undergo significant disulfide cross-linking to impart a structural rigidity to the outer membrane [21]. The replicative cycle inside the host cell ends when the chlamydia fills the cell and induces either lysis of the host cell releasing the EB cell type or extrusion of the inclusion again releasing the infectious EB cell type [22, 23].

The components of this unique developmental cycle impart two important pathogenic advantages to chlamydial infection. One, the inclusion membrane acts as a barrier between the bacteria and host cytosol and is thought to effectively hide the bacteria from host innate immune surveillance [24, 25]. Two, the infectious EB cell types small size and cross-linked outer membrane are likely key virulence adaptations that enhance the transmission and spread of the infection from person to person and from initial infection location to distal sites within the urogenital tract. The inclusion membranes' barrier function is a two-way street providing an immune evasion advantage but at the same time inhibiting the bacteria's access to the nutrients in the cell cytosol and restricting the delivery of effector proteins. The balance between these two opposing properties likely reflects important trade-offs in the biophysical characteristics of this unique replicative niche. The EB cell type is likely specialized to enhance infectivity in the differing niches it encounters. It's not clear what role the physical features of the EB cell type play in virulence, but increasingly, it is recognized that the EB cell type, although incapable of replication, can respond to environmental nutrients [26]. These results are consistent with the chlamydial EB being a metabolically responsive cell form that depends on maintaining active interactions with its environment to maintain infectivity.

Epidemiology

Chlamydia trachomatis is one of the most common bacterial sexually transmitted infections (STI) in the United States (US) among sexually active adolescents and young adults [27–29]. *C. trachomatis* can cause a variety of clinical syndromes

including urethritis, cervicitis, and oropharyngeal disease and has the potential to lead to long-term sequelae in women such as pelvic inflammatory disease (PID) and infertility. Adding to the public health implications of this infection, *C. trachomatis* increases the risk for acquiring HIV infection [30]. There are 15 serotypes of *C. trachomatis* with anogenital infection caused often by serotypes D-K and LGV (lymphogranuloma venereum) caused by L1, L2, and L3 [31].

In 2017, there were >1.7 million cases reported in the United States with the highest prevalence in adolescents and young adults under 25 years of age [29]. Most chlamydia infections are asymptomatic, so the number of infections identified and reported can increase as more people are screened even when incidence is flat or decreasing. The incidence *of C. trachomatis* has increased steadily in recent years, with a 6.9% overall increase in the number of cases from 2016 to 2017. During 2016–2017 alone, the rate among men increased 10.5%; however, during 2013–2017, rates of reported cases among men increased 39.3% compared with an 11.1% increase among women. There are twice as many chlamydia cases in women (687.4 cases per 100,000 females) as in men (363.1 cases per 100,000 males) in the United States; however, the number of cases increased by 3.8% in women and 10.5% in men from 2016 to 2017.

Rates of chlamydia vary by factors including age of patient, geographic region, race, and ethnicity (Fig. 13.1). Rates have been increasing in both young men and women since 2014 [32]. Among men, the age-specific rates of chlamydia cases were highest in the age group of 20–24 years old at 1705.4 cases per 100,000 males. Among women, the age-specific rates were highest in age group of 15–19 and 20–24 years and increased over the last 3 and 4 years, respectively. The rate among 15–19-year-olds increased 6.5% during 2016–2017, with a total increase of 10.7% during 2014–2017 (2949.3 to 3265.7 cases per 100,000 females). Black men and women are disproportionately affected by the disease with 5.6 times higher rates of chlamydia cases among Blacks than that among Whites (1175.8 and 211.3 cases per 100,000 population, respectively). Rates of reported cases are also high among

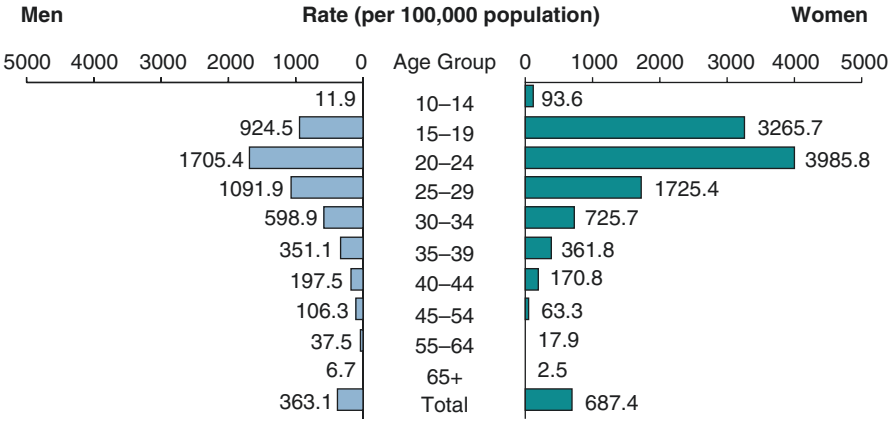


Fig. 13.1 Rates of reported cases by age group and sex, United States, 2017 [29]

Table 13.1 Prevalence of genital *Chlamydia trachomatis*[a] infection among persons aged 14–39 years, by selected characteristics — National Health and Nutrition Examination Survey, United States, 2007–2012 [34]

Characteristic	Sample size	Prevalence (%)	(95% CI)	Prevalence ratio	(95% CI)
Total	**8330**	**1.7**	**(1.4–2.0)**		
Sex					
Male	4181	1.4	(1.1–1.8)	0.7	(0.5–1.1)
Female	4149	2.0	(1.5–2.5)	1.0	
Age group (yrs)					
14–19	2724	2.4	(1.7–3.1)	1.0	
20–24	1456	2.9	(2.1–3.6)	1.2	(0.8–1.7)
25–39	4150	1.1	(0.7–1.4)	0.4	(0.3–0.8)
Race/ethnicity[b]					
Mexican American	1640	2.3	(1.4–3.1)	2.9	(1.7–5.1)
Black, non-Hispanic	1887	5.2	(4.0–6.4)	6.7	(4.3–10.6)
White, non-Hispanic	3019	0.8	(0.5–1.1)	1.0	
Poverty-to-income ratio[c]					
<100%	1490	2.3	(1.5–3.0)	1.5	(1.1–2.0)
≥100%	3615	1.6	(1.2–2.0)	1.0	
Current health insurance[d]					
Covered	5753	1.6	(1.3–1.9)	0.8	(0.6–1.1)
Not covered	2553	2.0	(1.5–2.5)	1.0	
Education[e]					
≤High school/GED	3092	2.7	(2.1–3.4)	2.4	(1.6–3.6)
>High school/GED	3371	1.1	(0.8–1.5)	1.0	
Marital status[e]					
Never married	2131	2.3	(1.7–3.0)	2.8	(1.8–4.6)
Divorced/widowed/separated	429	3.0	(0.9–5.2)	3.7	(1.6–8.8)
Married/living with partner	3043	0.8	(0.5–1.2)	1.0	
Currently using oral contraceptives/Depo-Provera[f,g]					
Yes	553	1.9	(0.7–3.1)	0.8	(0.4–1.6)
No	2331	2.3	(1.7–3.0)	1.0	
No. of sex partners in last year[g]					
0	402	1.8	(0.6–3.0)	0.6	(0.3–1.1)
1	3727	1.4	(1.1–1.7)	0.4	(0.3–0.7)
≥2	1686	3.2	(2.2–4.2)	1.0	
Age at first sex[g]					
<14 yrs	779	2.6	(1.5–3.8)	1.4	(0.9–2.4)
≥14 yrs	5062	1.8	(1.5–2.2)	1.0	

(continued)

Table 13.1 (continued)

Characteristic	Sample size	Prevalence (%)	(95% CI)	Prevalence ratio	(95% CI)
Past STD diagnosis[g,h]					
Yes	579	1.9	(0.8–3.0)	0.8	(0.4–1.7)
No	1564	2.3	(1.4–3.3)	1.0	

Abbreviations: *CI* confidence interval, *GED* General Education Development certification, *STD* sexually transmitted disease

[a]Prevalence estimates-based urine specimen tested using the Hologic/Gen-Probe Aptima assay

[b]Data for persons of other racial/ethnic groups, including other race, Hispanic ($n = 925$), and persons of multiple race/ethnicity ($n = 859$) are not presented but are included in overall analyses

[c]Ratio of family income to poverty level as defined by the US Census Bureau

[d]Based on response to the question, "Are you covered by health insurance or some other health-care plan?"

[e]Among persons aged ≥18 years

[f]Among females

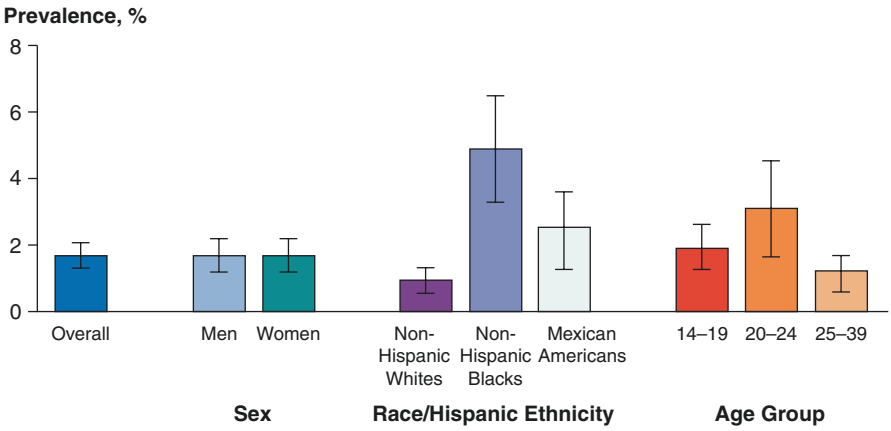
[g]Among persons who answered "yes" to the question "Have you ever had vaginal, anal, or oral sex?" ($n = 5848$)

[h]Participants who have been told by a doctor or other health-care professional in the last 12 months that they had chlamydia or gonorrhea or have ever been told they have herpes or genital warts

American Indians/Alaska Natives (3.4 times higher), Hispanics (1.9 times higher), and Native Hawaiians/Other Pacific Islanders (3.3 times higher) than the rates among Whites [29].

The National Health and Nutrition Examination Survey (NHANES) is a nationally representative survey of the US civilian, noninstitutionalized population that provides an important measure of chlamydia disease burden in respondents aged 14–39 years [4]. One NHANES study from 2013 to 2016 demonstrated that the overall prevalence of chlamydia among persons aged 14–39 years was 1.7% (95% confidence interval [CI]: 1.3–2.1). Among sexually active females aged 14–24 years, the population targeted for screening, prevalence was 4.3% (95% CI: 2.7–5.8), with the highest prevalence among Mexican American females (10.0%, 95% CI: 4.0–15.9) [29] (Fig. 13.2). A substantial number of infections are seen even among sexually active participants reporting only one partner in the last year [34]. With regard to certain high-risk populations, a cross-sectional analysis of chlamydia prevalence from incarcerated persons entering selected juvenile facilities was high at 14.3% for women and 6% for men. Incarcerated persons are more likely to report multiple partners, unprotected sex, history of substance abuse, and commercial sex work or difficulty accessing care and therefore at high risk for STIs including chlamydia [35–37].

While *C. trachomatis* often infects the urogenital tract, extragenital sites such as the oropharynx and rectum are emerging as important anatomic reservoirs of chlamydial disease burden in both men and women. Infections at these extragenital sites are often asymptomatic. A review of 80 studies from 5 international sites published between 1981 and 2015 focusing on extragenital infection reported a range of prevalence for rectal chlamydia of 2.0–77.3% and pharyngeal chlamydia of 0.2–3.2% in



Note: Error bars indicate 95% confidence intervals. Overall prevalence estimates include all race and Hispanic ethnicity groups, including those not shown separately.

Fig. 13.2 Chlamydia — Prevalence Among Persons Aged 14–39 Years by Sex, Race/Ethnicity, or Age Group, National Health and Nutrition Examination Survey, 2013–2016 [29, 33].

women, rectal chlamydia of 2.1–23% and pharyngeal chlamydia of 0–3.6% in MSM, and rectal chlamydia of 0–11.8% and pharyngeal chlamydia of 0–22% in limited data in MSW [38]. Specifically in the United States, one study at an STD clinic in Seattle, Washington, demonstrated pharyngeal chlamydia infection at 2.3% and rectal chlamydia infection at 11.9% [39]. Differences in prevalence of *C. trachomatis* infections at these extragenital sites were often seen due to different clinical settings and methods of diagnosis.

Despite expansion of testing, many young people who are at risk are still not being tested, with fewer than half of sexually active young women screened annually despite high prevalence and incidence of disease in this group. There is also data to support screening programs for chlamydia infection in women, in order to help prevent adverse sequelae such as PID [40]. However, studies have demonstrated suboptimal chlamydia screening and rescreening rates in both men and women, ranging from 22.3% to 44%, in a variety of clinical settings [41–44].

The high prevalence of chlamydial infection in the United States among adolescents and young adults is attributable to a variety of reasons including asymptomatic infection, lack of adequate screening, lack of familiarity with this infection among treating clinicians, and a paucity of available facilities for easy detection and treatment. Furthermore, there is a need for programs focused on screening high-risk patients, contact tracing, and rapid treatment of infected individuals. Most of cases of chlamydia (over 75%) have been reported outside of STD clinics, mostly from private physicians and health maintenance organizations, emphasizing the need for testing and treatment in a variety of settings (Fig. 13.3) [29]. There is therefore a clear need for training of a wide range of primary care providers, in order to enhance

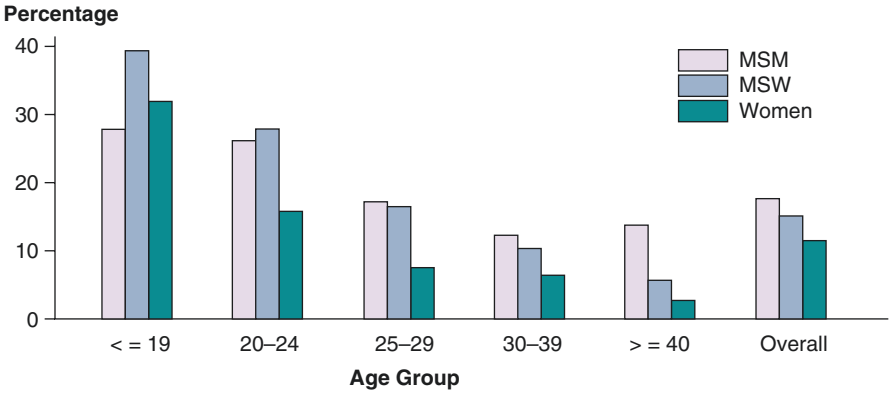


Fig. 13.3 Chlamydia — Proportion of STD Clinic Patients Testing Positive∗ by Age Group, Sex, and Sexual Behavior, STD Surveillance Network (SSuN), 2017 [29]. ∗ Proportions represent the overall average of the mean value by jurisdiction. † Results are based on unique patients with known sexual behavior (n = 95,167) attending SSuN STD clinics who were tested ≥1 times for chlamydia in 2017. Acronyms: MSM = Gay, bisexual, and other men who have sex with men (collectively referred to as MSM); MSW = Men who have sex with women only

awareness of national recommendations for STI screening and improve rates of routine STI screening and health education among at-risk populations such as adolescents and young adults.

Screening

The majority of chlamydia infections are asymptomatic, making routine screening of high-risk individuals critically important for controlling and preventing disease transmission to protect both individuals and the public health. Detection and treatment of infection can prevent serious sequela in women, and screening programs have contributed to declines in rates of PID [40, 45, 46]. The 2015 CDC STD treatment guidelines outline screening recommendations for men and women, including adolescents [47]. Adolescents and young adults who initiate sex early in adolescence, those who are incarcerated or in detention facilities, those who use injection drugs, those evaluated in STD clinics, young men who have sex with men (MSM), and those with multiple sex partners are considered high risk and should be screened routinely for infection [29].

No state in the United States requires parental consent for STI care, but healthcare providers should check with local and state recommendations regarding the details of STI services and parental notification. They should also be aware of insurance claims and notification to beneficiary of services performed when treating the adolescent and young adult community in the geographic area. However,

these confidentiality concerns must be balanced against the benefits to the individual and society. If patients do not have access to care or clinicians do not screen, many infections go undiagnosed, unreported, and untreated leading to the spread of disease.

Heterosexual Individuals

The USPSTF and the CDC recommend screening for chlamydia in sexually active females ≤24 years and in older women at increased risk for infection, such as a new sex partner, multiple sex partners, or sex partners with an STI [47, 48]. While data to assess screening for chlamydia in heterosexual men is lacking, in areas with high prevalence of chlamydia, screening of young heterosexual men can also be considered. This can include screening in adolescent clinics, correctional facilities, STD clinics, or geographic areas with a high prevalence of chlamydia infection rates [48–50]. Despite the recommendations made by USPSTF and CDC regarding screening heterosexual individuals, rates of testing for *C. trachomatis* infection are still unfortunately low [51–54]. There are no recommendations regarding screening of extragenital sites in heterosexual individuals, such as rectal or oropharyngeal chlamydia infection, but these infections do occur and are often asymptomatic. Providers should therefore inquire about oral and anal sexual practices and test at extragenital sites as indicated by the individual patient's sexual practices.

Pregnant Women

Mother-to-child transmission of chlamydia can cause severe complications in the neonate, including conjunctivitis and pneumonia. Screening for *C. trachomatis* infection in pregnant women is therefore extremely important [48]. It is recommended that all pregnant women <25 years be tested for chlamydial infection and gonorrhea during the first prenatal visit and retested during the third trimester [55]. If a pregnant woman is found to have evidence of chlamydia infection, repeat NAAT testing for eradication of the disease should be done 3–4 weeks after completion of therapy to document cure of infection and again 3 months after treatment. Repeat testing and documentation of cure is recommended in pregnant women as persistent or a new infection with *C. trachomatis* can be transmitted to the neonate during parturition. In addition to the risk of neonatal pneumonia and conjunctivitis, studies have shown that treatment of chlamydial infection is associated with significantly lower rates of preterm delivery, early rupture of membranes, and infants with low birth weight compared with no treatment or treatment failure [56].

MSM (Men Who Have Sex with Men)

In this population, there is increased risk for HIV and STDs, and screening is recommended at least yearly for urethral infection in men who have insertive intercourse and/or rectal infection in those who have receptive anal intercourse [47]. In those persons with multiple or anonymous partners, sexual partners with multiple partners, or other high-risk factors, 3–6 month screening for *C. trachomatis* is recommended [57]. Gay-focused community-based organizations can serve as valuable partners in helping to reach young MSM who may not be tested elsewhere. Other than urethral chlamydia infection, rectal and oropharyngeal chlamydial infection can be important anatomic areas of infection and routes of transmission to uninfected partners. Although testing for *C. trachomatis* pharyngeal infection is not specifically recommended by the CDC [47], extragenital infections are common in the MSM population. There have been reported cases of oropharyngeal to genital transmission of infection, and therefore screening can be considered, especially in highly prevalent populations [38, 39, 58–65]. Furthermore, rectal chlamydia infection has been associated with increased risk of HIV acquisition among MSM. While NAAT is not currently cleared by FDA for pharyngeal testing, many public health departments and other providers utilize NAAT-based pharyngeal, rectal, and urethral screening for chlamydia among the MSM population. Health-care providers should be aware of the significant public health implications associated with chlamydia: (1) multiple infections with gonorrhea or chlamydia are associated with increased risk of HIV infection among MSM [66, 67], and (2) incidence of STDs has been shown to decline with frequent, routine STD testing and risk reduction counseling in high-risk populations [68].

WSW (Women Who Have Sex with Women)

While historically WSW were considered to be low risk for STIs [69, 70], recent data suggests that assessment and screening of STIs among WSW is an important part of their sexual health [71–74]. There is data to suggest this population is still at risk for STIs, particularly adolescent and young adult WSW and those who also have male partners [75–78]. A study evaluating young women ages 18–24 years reported that bisexual students were most likely to have an STI in the past year; of note, even among those who reported only female partners, 6% had evidence of an STI [78]. In another study, a high rate of *C. trachomatis* infection was seen in African American WSW who participated in exclusive sexual activity with women (13.5%), and an even higher rate (35%) was demonstrated if these women had sex with men as well [79]. Another study among WSW ages 15–24 years old showed positive chlamydia cases among WSW and WSMW (women who have sex with men and women) at 7.1% compared to WSM (women who have sex with men) at 5.3%. This provides evidence to suggest that *C. trachomatis* is common among women reporting same-sex sexual behavior, especially in the adolescent and young adult age group. Health-care providers should implement STI screening according to the general guideline for young women and cannot assume that WSW are at low risk for STIs [80].

Transgender Patients

While there are few studies of *C. trachomatis* infection specifically in transgender men and women, providers should discuss patient anatomy and sexual behavior with these patients and provide screening according to risk behavior and guidelines [81]. It is recommended that transgender patients should be assessed closely for STD- and HIV-related risks and screened accordingly based on behavioral history and sexual practices.

HIV

For those with HIV-positive status, all men and women should be screened for chlamydia, in addition to other STIs, initially upon entering into care and at least annually, with more frequent follow-up testing (3–6 months) depending on risk behavior [81–83]. Given high reinfection rates in this population, retesting for chlamydia infection is indicated at 3 months after treatment, not to document cure but to assess for new infection. Specifically, MSM with HIV infection are at increased risk for STDs [68]; therefore, screening for syphilis, gonorrhea, and chlamydia is an important part of primary care by health-care providers.

Persons in Correctional Facilities

There are high rates of chlamydia infection, as well as other STIs, in both men and women ≤35 in juvenile and adult detention facilities [84]. The rates are higher in women than in men which is concerning given the long-term complications of chlamydia infection that can occur in women. This patient population might have had limited access to medical care or engage in high-risk behaviors for STIs. Therefore, universal screening for chlamydia in women ≤35 entering correctional facilities is recommended. For men, it is recommended to screen for chlamydia among <30 years old at intake into jails and other correctional facilities [49, 81].

Coinfections

Persons infected with *N. gonorrhoeae* are frequently coinfected with *C. trachomatis* and other STDs; therefore, it is important to screen for these infections, including gonorrhea, syphilis, and HIV [85, 86]. Women with bacterial vaginosis have also been shown to be at increased risk for chlamydia infection [87].

Repeat Infections

Several studies have shown there are high rates of repeat infection several months after initial chlamydia infection, often due to unprotected sex with an untreated sex partner or a new sex partner. In men, 13% had evidence of repeat infection within 4 months of initial diagnosis, and among female adolescents, 26.3% had reinfection within one year [88–90]. Repeat infection with chlamydia is associated with elevated risk for PID and other complications in women. Therefore, rescreening for this STI is an underutilized but important intervention in those persons with a past history of chlamydia infection in many primary care settings. The CDC STD treatment guidelines recommend men and women who have been treated for *C. trachomatis* should be retested approximately 3 months after treatment (or whenever persons next present for medical care if retesting at 3 months is not possible) [47], regardless of whether patients believe sex partners were treated. Test-of-cure using NAAT at 3–4 weeks is not routinely recommended for patients except in cases of pregnant women, questionable medication adherence, persistence of symptoms, or suspected reinfection.

Clinical Features

Infections with *C. trachomatis* are often asymptomatic but can lead to both acute symptoms and long-term health consequences such as PID and infertility in women and increased risk of HIV transmission in both sexes [91]. In men, the urethra is the most common site of infection, while in women, infection is often in the urethra and cervix. Adolescent and young adult women often have undiagnosed chlamydial infection. The asymptomatic nature of disease facilitates transmission of the bacteria between partners given a large reservoir of untreated persons who do not know they are infected.

Infections in Women

While chlamydial infections in women are often asymptomatic, the disease can result in urethritis, cervicitis, pelvic inflammatory disease, ectopic pregnancy, and ultimately infertility [92, 93]. Some symptoms in women mimic that of a urinary tract infection (painful or burning urination), and abnormal vaginal discharge or bleeding can also be seen. On speculum examination, patients with cervicitis will have cervical erythema, endocervical discharge, and/or a friable cervix (easily induced bleeding) [94, 95]. Providers should suspect an STI in women with urethritis, especially those with a new sex partner. Symptoms of PID include fever, pelvic or abdominal pain, and adnexal/cervical motion tenderness [92, 94] with the potential to scar and produce adhesions and inflammation in the fallopian tubes, ovaries,

and endometrial lining leading to infertility [96]. While the rate of progression to PID in the general, asymptomatic population appears to be low, in some high-risk settings, 2–5% of untreated women can develop PID [97–99]. If an infected mother passes the infection to infants in delivery, potential consequences of blindness and pneumonia in the infant can occur.

Infections in Men

In men, chlamydia infection is a cause of urethritis, epididymitis, oropharyngeal infection, and acute proctitis in MSM who practice receptive rectal intercourse. *C. trachomatis* accounts for approximately 20–50% of cases of NGU (nongonococcal urethritis) [100]. Often, men present with symptoms of dysuria, urethral discharge, and urethral discomfort. The discharge which can be sparse might be mucopurulent, cloudy, or clear. Patients might have erythema of the urethral meatus with localized lymphadenopathy. In younger men, *C. trachomatis* is a common cause of acute epididymitis, in which patients present with testicular or scrotal pain and tenderness on exam [101]. Epididymitis is usually associated with urethritis; the latter is often asymptomatic.

Anorectal Infection

Anorectal infection can occur in men or women who practice receptive rectal intercourse. Like urethral infection, it can be asymptomatic but also has the potential to lead to severe proctitis or inflammation of the rectum. Anorectal chlamydia infection often presents with anal pruritus, mucopurulent or bloody rectal discharge, anal pain, constipation, or tenesmus. If patients present with symptoms of proctitis, they should have anoscopy and evaluated for STIs. Treatment of anorectal *C. trachomatis* infection appears to have more efficacy with a doxycycline-based regimen rather than a single dose of azithromycin [102] (outlined further in Treatment section of chapter). Sigmoidoscopy, when performed (generally to rule out other causes of proctitis), might demonstrate friable rectal mucosa, and a rectal gram stain would be expected to show elevated polymorphonuclear leukocytes (PMNs).

Oropharyngeal Disease

The pharynx can be a site of chlamydial infection in either men or women, if oral-genital contact occurs [59]. While this presentation is also often asymptomatic and underdiagnosed due to inadequate screening, patients can present with symptoms of pharyngitis including sore throat, fever, and tender cervical adenopathy. If infected

at this anatomic site, patients have the potential to transmit this infection to uninfected partners through oral-genital contact [103, 104].

LGV (Lymphogranuloma Venereum)

LGV is caused by chlamydial serotypes L1, L2, and L3 – like other strains of chlamydia, these serotypes are also transmitted through unprotected vaginal, anal, or oral sexual contact. The classic presentation of LGV includes typically painless genital ulcers with tender femoral and inguinal adenopathy. LGV can also manifest as proctitis in those practicing receptive anal intercourse – symptoms may include diarrhea, abdominal cramps, rectal pain, mucoid/bloody rectal discharge, and/or fever [105, 106]. LGV proctitis can lead to serious sequelae if left untreated, such as perirectal abscess, fistulas, and strictures [107, 108]. Coinfections of other STIs with LGV is common. Due to the increase of LGV in MSM populations in the last 10–15 years, health-care providers should consider LGV in the diagnosis when sexually active patients present with proctitis or inguinal/femoral lymphadenopathy, especially if they are HIV-seropositive MSM.

Diagnostic Testing

While empiric therapy is recommended in a patient with symptoms suggestive of chlamydia, diagnostic testing should always be performed to confirm *C. trachomatis* infection. This testing facilitates the evaluation and treatment of both patients and sexual contacts. Chlamydia trachomatis is a reportable disease in every state which helps with public health efforts including monitoring, treatment, and prevention. Clinicians should familiarize themselves with local reporting requirements by local STI programs, as well as national guidelines.

Diagnostic testing for *C. trachomatis* rely primarily on molecular testing by PCR. Serologic tests are not widely used, other than to help support the diagnosis of LGV since baseline prevalence of antibody to *C. trachomatis* is high in certain populations and IgM Ab often cannot be demonstrated within the time frame of disease. In men with urethritis, a gram stain showing gram-negative intracellular diplococci (suggesting *N. gonorrhoeae*) is a rapid way to distinguish NGU from gonorrheal infection; however, microscopy alone cannot diagnose chlamydia infection. There is not enough data to support the use of gram stain on endocervical specimens from women or pharyngeal or rectal specimens from men or women.

The recommended test to diagnose chlamydia infection in both men and women is NAAT (nucleic acid amplification testing) [65, 109]. The FDA has approved

NAAT testing for the diagnosis of *C. trachomatis* testing in genitourinary tract specimens [110]. In women, this can be done by testing first-catch urine or collecting swab specimens from the endocervix or vagina. In men, urethral swabs or first-catch urine specimens can be tested. Extragenital sites, such as oropharyngeal and rectal specimens, have not been cleared by the FDA for detection of chlamydia, but most laboratories have performed Clinical Laboratory Improvement Amendment (CLIA)-compliant validation studies and may offer NAAT for extragenital specimens [58, 65, 110]. All cases of urethritis in men should be screened for *C. trachomatis* by NAAT on first-catch urine, and MSM should be tested for *C. trachomatis* from any potentially exposed site (e.g., rectum, throat) [103].

Point-of-care tests can help facilitate early treatment, but they have reduced sensitivity and specificity compared with NAAT testing [111]. However, rapid NAAT tests for chlamydia are available, can provide testing with same-day results, and might be of benefit to use in the adolescent and young adult population. The Cepheid GeneXPert CT/NG assay is a chlamydia rapid NAAT with high sensitivity and specificity of >97% for *C. trachomatis* and is approved for urine and endocervical/vaginal swabs [112]. Self-collection of swabs as an alternative to clinician-collected swabs is reliable and one way to help expedite or simplify screening in both men and women that is acceptable to patients [113–116].

Women with cervicitis should be tested for chlamydial infection and assessed for signs of PID. The finding of >10 WBC per high power (400X) field is consistent with endocervical inflammation caused by *C. trachomatis* or *N. gonorrhoeae,* but this is not diagnostic [117]. NAAT testing on vaginal swab fluid collected by clinician or the patient has higher sensitivity than urine, and for women being evaluated with a speculum exam, NAAT testing can be done on endocervical swabs [118].

Genital lesions and rectal specimens can be tested for *C. trachomatis* in the setting of LGV or other anorectal disease by NAAT if CLIA validation studies have been done in the laboratory and are the preferred method of detection. Diagnosis of LGV is based on clinical suspicion and rates seen in the community while excluding other causes of symptoms. Based on clinical presentation (e.g., symptoms of proctitis) with or without a positive NAAT, patients with findings of LGV should be treated empirically.

Recurrence of infection occurs frequently in adolescents and young adults of both sexes [90, 119]. Therefore, if a patient tests positive for chlamydia, recommendations are to rescreen that person 3 months after treatment to evaluate for new STIs [47]. One study demonstrated that 13% of men with *C. trachomatis* infection in urban centers ages 15–35 years of age were reinfected [88]. Among female adolescents in school-based health centers, the incidence of reinfection was also high, supporting the recommendation to rescreen adolescents frequently (both men and women) [89]. Early repeated chlamydial infections (<3 months) in adolescent women were often by the same genotype than later repeated infections [90], suggesting that most repeated infections may result from failure of sex partners to

receive treatment. Despite these findings, studies have shown that the repeat testing recommendations are infrequently followed. In an analysis of chlamydia testing data from a large US laboratory from 2008 to 2010, positivity rates were highest among female adolescents, and retesting rates of persons with a history of infection were suboptimal, with only 22.3% of men and 38.0% of nonpregnant women retested. Of pregnant women, although 60.1% with a positive test were retested, only 22.0% received a test-of-cure within the time frame recommended in the CDC STD treatment guidelines [43].

If follow-up cannot be insured in patients presenting with symptoms consistent with chlamydia infection, they should be treated presumptively until results of testing are available. Cases should be reported to the health department per state requirements. Test-of-cure or repeat testing 3–4 weeks after completing therapy is no longer routinely recommended except in specific situations such as pregnant women, suspected nonadherence to treatment, persistent symptoms in a patient or partner, and concern for reinfection. Of note, however, positive NAAT testing within 3 weeks might reflect the presence of nonviable organisms; therefore, repeat testing less than 3 weeks after a positive result is generally not recommended [110].

Treatment

Antibiotics with good intracellular penetration must be used for *C. trachomatis* infections, which also necessitate either a long half-life or a prolonged course of therapy. Treatment is critical to prevent health complications in the individual, reinfection of sex partners, and transmission to uninfected individuals and infants in pregnant women [98]. The most active agents against *C. trachomatis* include rifampin, tetracyclines, macrolides, sulfonamides, some fluoroquinolones, and clindamycin [120] (Table 13.2).

Recommended Regimens

Oral doxycycline 100 mg twice daily for 7 days and azithromycin as a single-dose therapy (1 gram taken orally) in directly observed therapy are both first-line recommendations for treatment of chlamydia infection of the urogenital tract. Alternative regimens are listed in Table 13.3a and include erythromycin, levofloxacin, and ofloxacin. Erythromycin might have a higher rate of GI side effects and lower efficacy [121]. Azithromycin (but not doxycycline) can be administered in pregnant women, who – as noted above – should have repeat NAAT for test-of-cure in 3–4 weeks. Persons with chlamydia should be instructed to abstain from sexual intercourse for 7 days after treatment completion or until resolution of symptoms, whichever occurs last [47].

Table 13.2 MIC of selected antimicrobial agents against *Chlamydia trachomatis* and *C. pneumoniae* [120]

Antimicrobial	*C. trachomatis*	*C. pneumoniae*
FDA-approved drugs		
Doxycycline	0.031–0.25	0.015–0.5
Tigecycline	0.03–0.125	0.125–0.25
Erythromycin	0.016–2	0.015–0.25
Azithromycin	0.6–2	0.05–0.25
Clarithromycin	0.015–0.125	0.004–0.125
Clindamycin	2–16	–
Ciprofloxacin	0.5–2	1–4
Levofloxacin	0.12–0.5	0.25–1
Moxifloxacin	0.5–1	0.125–1
Rifampin	0.005–0.25	0.0075–0.03
Trimethoprim	≥128	≥128
Sulfamethoxazole	0.5–4	≥500
Gentamicin	500	500
Vancomycin	1000	1000
Investigational drugs		
Solithromycin (CEM-101)	0.125–0.5	0.25–1
Sitafloxacin	0.031–0.063	0.031–0.125
Nemonoxacin	0.03–0.125	0.03–0.125
Delafloxacin	–	0.06–0.125
AZD0914	0.06–0.5	0.25–1
Rifalazil	0.00125–0.0025	0.00125
MIC range (μg/ml)		

Table 13.3a Treatment of *Chlamydia trachomatis* infection in adolescents and young adults and pregnant women [47]. Adolescents and young adults

Recommended regimens		
	Azithromycin	1 gram orally in a single dose
	Doxycycline	100 mg orally twice a day for 7 days
Alternative regimens		
	Erythromycin base	500 mg orally four times a day for 7 days
	Erythromycin ethylsuccinate	800 mg orally four times a day for 7 days
	Levofloxacin	500 mg orally once daily for 7 days
	Ofloxacin	300 mg orally twice a day for 7 days

There is some evidence of heterotypic in vitro resistance to doxycycline [122]. However, doxycycline has been shown to be quite effective in clearing *C. trachomatis* infections, and recent studies have shown better efficacy with doxycycline compared to azithromycin for treatment of NGU and chlamydia rectal disease [102,

122–126]. A meta-analysis evaluating treatment for rectal chlamydia demonstrated pooled efficacy for doxycycline at 99.6% compared to azithromycin at 82.9% [102]. A summary of 23 studies found there might be small increased efficacy for doxycycline compared with azithromycin for the treatment of urogenital chlamydia as well, but more data are needed in this area [124, 125]. However, suboptimal adherence to the multiday dosing of doxycycline might contribute to poor treatment outcomes for *C. trachomatis* infection in men with NGU, although nonadherence was not significantly associated with clinical failure overall [127]. Compliance with a 7-day antibiotic regimen might be especially challenging in the adolescent and young adult population; therefore, health-care providers should assess their patient's ability to comply with therapy and weigh the risks and benefits of 7 days of doxycycline versus one-time azithromycin therapy. A randomized control trial to evaluate treatment efficacy of azithromycin versus doxycycline for the treatment of rectal chlamydia among MSM is pending [128].

LGV infection with serotypes L1, L2, and L3 can lead to serious consequences if left untreated. These include colorectal fistulas, strictures, and even elephantiasis. Relative to other chlamydial infections, LGV requires a prolonged course of therapy [121]. For LGV, the treatment of choice is doxycycline 100 mg orally twice daily for 21 days. Erythromycin 500 mg orally four times daily for 21 days is an alternative regimen that can be used in pregnancy (Table 13.3b) [47].

Sexual partners should also be referred for evaluation, testing, and treatment if they have had sexual contact with the patient within 60 days of symptom onset or diagnosis. *Expedited partner therapy* (EPT) also known as *patient-delivered partner therapy* (PDPT) is legal in most states and refers to the process of giving prescriptions or medications to the patient for delivery to their partner(s), without direct evaluation of the partner by the treating clinician. The impact of prescriptions on sex partner treatment using expedited partner therapy for *C. trachomatis* was recently evaluated in young women ages 15–25 years, and prescription-EPT and medication-EPT chlamydia showed comparable rates of partner treatment [129]. These methods of partner treatment are recommended by the CDC STD guidelines to be offered to heterosexual

Table 13.3b Treatment of *Chlamydia trachomatis* infection in adolescents and young adults and pregnant women [47]. Pregnant women

Recommended regimens		
	Azithromycin	1 gram orally in a single dose
Alternative regimens		
	Amoxicillin	500 mg orally three times a day for 7 days
	Erythromycin base	500 mg orally four times a day for 7 days
	Erythromycin base	250 mg orally four times a day for 14 days
	Erythromycin ethylsuccinate	800 mg orally four times a day for 7 days
	Erythromycin ethylsuccinate	400 mg orally four times a day for 14 days

patients with chlamydia infection when the provider cannot ensure that all sex partners from the prior 60 days will be otherwise treated, only if this practice is legal in their state (www.cdc.gov/std/ept) [47]. Patients assigned to expedited treatment of sexual partners are significantly more likely than those assigned to standard referral of partners to report that all of their partners are treated. They are also significantly less likely to report having sex with an untreated partner and are shown to have high levels of acceptability in the adolescent population [130, 131]. Studies have shown that EPT/PDPT can increase partner treatment rates, thereby decreasing the rate of reinfection, with potential to decrease *C. trachomatis* incidence at the population level [131–134]. The main limitation of EPT is that it misses an opportunity to test partners for coexisting infections that may require treatment – including gonorrhea, syphilis, or HIV. For this reason, the recommendation is for EPT to be used in low HIV prevalence settings, for heterosexual populations. EPT chlamydia is not currently recommended for MSM with chlamydia given the high risk of undiagnosed concomitant HIV infection and other STDs in this patient population. For all patients, full evaluation and testing of a partner of an infected patient is ideal, and all persons with chlamydia should be encouraged to notify sex partners and to seek treatment.

Prevention

There is no vaccine that prevents chlamydia infections. Abstinence from oral, vaginal, and anal sex and a monogamous relationship with a partner known to be uninfected are the most effective ways to prevent disease. Male and female condoms, when used consistently and correctly, can significantly decrease the rate of STIs, including chlamydia [135].

As a high proportion of chlamydia infections impact adolescents and young adults, public health efforts focused on prevention in this age group are extremely important to reduce the number and impact of STIs over the course of their lives. Health-care providers play an important role in these efforts, including obtaining detailed sexual histories from patients and providing risk reduction and prevention counseling in a nonjudgmental way to all sexually active adolescents [136–138]. Programs to institute strategies for chlamydia screening, especially in asymptomatic individuals, as well as effective diagnosis, treatment, and follow-up of patients and their partners can help with prevention and control of this disease. In adolescents and young adults, patients might be marginalized and may not have access to care or psychosocial barriers that make access to care difficult.

An analysis of 31 trials suggested that high-intensity counseling (>2 hours) reduced STI incidence in adolescence in primary care and related settings [137]. While data are sparse, less intensive interventions also have the potential to reduce STIs in adolescents and young adults [139–141]. Both enhanced (quarterly, high intensity, interactive) and brief counseling groups lowered STD incidence at 3 and 6 months, and 30% fewer participants had new STDs in the enhanced counseling group at 6 months [142]. Sexual risk reduction interventions

should provide information on all STIs, including HIV, as well as prevention strategies such as condoms, regular screening, and pre-exposure prophylaxis for HIV if indicated.

Early sexual education and STD testing of all sexually active adolescents is an important part of prevention. For this particular population, barriers to screening that have been identified include lack of health insurance coverage or coverage under a parent, lack of regular access to health care, as well as the difficulties of identifying adolescents who have been sexually active [143–147]. The majority of women initiate sexual activity during adolescence, and even those youth who have little sexual experience (e.g., less than one year) or those with few lifetime partners, the prevalence of any STI is quite high. However, despite recommendations and high prevalence of STIs in this sexually active young female population, only 42% of eligible young women received annual chlamydia screening in 2007 in US commercial and Medicaid health plans [51], recognizing there is a great need for chlamydia screening to protect young women from sequelae of this infection [148]. Health-care providers should educate young patients about prevention strategies to lower STI risk by using condoms consistently and correctly, safer sex, and how to obtain medical care for STIs without parental consent in their geographic area [142].

As chlamydia is common and infections are usually asymptomatic, health-care providers should routinely screen sexually active young men and women according to guidelines, provide prompt treatment for infected persons, and ensure that infected patients' sex partners receive timely treatment to prevent reinfection.

Case Conclusion

The patient's presentation is consistent with acute Chlamydia trachomatis urethritis given his penile discharge, burning with urination, and mild inguinal lymphadenopathy. While these symptoms are classic for urethritis, the majority of patients with chlamydia infection are asymptomatic. Therefore, it is a major public health problem as persons might not realize they have the disease and are likely to unknowingly spread *C. trachomatis* to previously uninfected individuals. In men, symptomatic chlamydia infection causes urethritis; in women, it can cause urethritis or vaginitis. *C. trachomatis* can also colonize the oropharynx or rectum, as it can be transmitted through oral, vaginal, or anal sex. Complications in women can lead to pelvic inflammatory disease and infertility. Treatment involves therapy as soon as possible. Both this patient and his partners should be treated, even if they don't have evidence of symptomatic disease. Given this patient's risk factors of multiple sex partners as well as positive chlamydia testing, he should be screened at least every 3–6 months for sexually transmitted infections, including HIV. Barrier methods should be advised to protect the patient and his partners against other sexually transmitted infections.

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Chapter 14
Trichomonas vaginalis

Cherie Priya Dhar

Case Study
A 15-year-old previously healthy female presents to the emergency room with vaginal discharge. She reports having this symptom for 2 weeks. She denies any malodor and has minimal pruritis but is concerned about the copious amount of discharge. She was recently seen at her pediatrician's office where wet mount microscopy was reportedly negative for yeast, clue cells, and trichomonads. Urine nucleic acid amplification testing at that time was also negative for *Neisseria gonorrhea* and *Chlamydia trachomatis*. She was given instructions for vaginal hygiene, which she has been following, but the discharge has persisted. She reports sexual activity with one monogamous male partner, who denies any symptoms and who has recently been "tested for everything" with negative results. She also reports dyspareunia which has persisted over the past 3 weeks.

Questions for Consideration
- How does *Trichomonas vaginalis* infection present?
- Who should be tested?
- How is trichomoniasis diagnosed?
- What is the treatment?
- Are there any complications?

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Epidemiology

Trichomonas vaginalis is the most prevalent nonviral sexually transmitted infection in the United States. The few studies that include adolescents and young adults show that *T. vaginalis* is a common pathogen in this population. According to the National Longitudinal Study of Adolescent to Adult Health (Add Health) data, the estimated prevalence of trichomoniasis in young adults in the United States was 2.3%, with young women (2.8%) more likely to be infected than young men (1.7%) [13]. Across age groups, *T. vaginalis* is more common in women than men. Unlike other sexually transmitted infections, rates of trichomonas are evenly distributed among sexually active females across age groups [10].

Populations at risk for trichomoniasis are similar as those at risk for other sexually transmitted infections. Up to 32% of incarcerated individuals and up to 17% of persons at STD clinics have *Trichomonas vaginalis* infection. In those persons infected with the human immunodeficiency virus (HIV), *Trichomonas* infection is twice as common compared to the HIV-negative population. *Trichomoniasis* is five times more prevalent among persons identified as Black (6.9%) as compared with White (1.2%), with the prevalence among Black women (13.3%) nearly ten times higher than the prevalence among White women (1.3%) [19]. Men who have sex with men have been demonstrated to have low rates of *T. vaginalis* infection [12].

Microbiology and Pathophysiology

Trichomonas vaginalis is a single-celled 9-by-7 micron pyriform-shaped protozoan with four flagella at one end, which it uses to propel itself, and a fifth embedded in its membrane. This motility helps to facilitate visualization of trichomonads with microscopy. It survives in moist areas of the body such as the urethra in males and females and the vulva and vagina in females. In an infected person, there are estimated to be 101 to 105 protozoa/mL of vaginal fluid [4]. It reproduces via binary fission, and this commonly occurs on the mucosal surface of genitourinary tracts of humans, causing local inflammation and microulcerations which lead to symptoms [4, 10, 17].

Trichomonas vaginalis is transmitted through coitus and humans are the only known natural host [4]. Of note, though not substantiated by large clinical trials, there have been case reports of nonvenereal transmission of trichomonas via contaminated bathwater [3], soaps and sponges, and towels [1].

Clinical Presentation

Trichomonas infects both males and females and causes symptoms in both sexes; however, 50–60% of infections in women are asymptomatic [6, 19]. In females, signs and symptoms can include itching and local erythema, dysuria, and/or vaginal

or urethral frothy discharge which may be yellow-green and malodorous. They may report dyspareunia or lower abdominal discomfort. Speculum exam may reveal an erythematous punctate cervix, also known as the "strawberry cervix" or colpitis macularis, although speculum exam in adolescents is no longer routinely performed for evaluation of simple vaginal discharge [4, 10].

Vaginal secretions have a normal pH of 3.8–4.5. Trichomonads may prefer a more alkaline pH and may be able to alter the vaginal pH in order to enhance their own survival [4, 10] though studies are still unclear. Some literature suggests that when estrogen levels decrease, such as during menses or in postmenopausal women, the vaginal pH increases making these times wherein females may be more susceptible to trichomoniasis [9]. Estrogen causes proliferation of vaginal epithelial cells which increases glycogen production. This glycogen is transformed into lactic acid by lactobacillus, rendering vaginal pH <4.5 [16].

Of men diagnosed with trichomoniasis, only 2.3% reported symptoms of urethral discharge or dysuria [13]. It rarely causes prostatitis or epididymitis [4, 10] though can occasionally present with inguinal lymphadenopathy [11]. Of note, there may be an association between infection with trichomonas and decreased sperm motility [22].

Coinfection with trichomoniasis and *Chlamydia trachomatis* is frequently observed. Although the overall prevalence of chlamydial infection is 4.2%, among persons with trichomoniasis, the prevalence of chlamydial infection is 12.7%, with the increased odds of co-occurrence more pronounced for women than men [13].

It remains unclear whether *T. vaginalis* can cause rectal or oral infection or whether these sites simply serve as reservoirs for *T. vaginalis*. Currently there is no recommended screening of these extragenital sites in any demographic or risk group.

Screening

Diagnosis of trichomoniasis requires a high index of suspicion, as there are currently no screening guidelines other than for women infected with HIV. Otherwise, per the 2015 CDC screening guidelines, screening of males and females can be considered by STD clinics and correctional facilities, commercial sex workers, or those with multiple partners [23]. There are no strict criteria for screening or treatment of asymptomatic persons because it is unclear whether this will decrease infection burden or adverse health events. Trichomonas is not a reportable infection in the USA [23]. Given the high burden of infection and association with HIV transmission and acquisition, screening should be highly considered in youth in detention centers, youth requesting STI testing, and in persons with multiple sexual partners or whom have previously been diagnosed with a sexually transmitted infection. In adult STI clinics, the prevalence of trichomonas infection approaches 25% [4] thus in this clinical setting, testing may be cost-effective in reducing overall disease burden. Additionally, testing should be completed in females who seek evaluation for lower abdominal pain and genitourinary concerns. One study of emer-

gency room patients showed a prevalence of STI of 25% in females presenting with these concerns, and trichomonas was the second most common STI diagnosed in this study [7].

Diagnostic Testing

There are several methods to detect *T. vaginalis*. The wet mount of vaginal secretions is the oldest form of detection; it requires the clinician to prepare a slide and use 40X microscopy magnification to detect the flagellated organism. This is done often in outpatient clinical settings with patient- or clinician-collected swabs *T. vaginalis* culture remains the gold standard of diagnosis – it has a specificity of 100% but lower sensitivity (75–96%); thus it is not widely used for detection. Additionally, culture requires the specimen to be placed in medium within 1 hour. Polymerase chain reaction detection is more sensitive than culture, but there is no FDA-approved kit for this [2].

There are two newer modalities of detection that are used more frequently in current clinical practice: a point-of-care (POC) rapid antigen detection test and nucleic acid amplification testing (NAAT). The POC test is an antigen detection test that is performed using vaginal secretions, with the benefit of giving a result within 10 minutes. The POC test has a higher sensitivity (82–95%) than the wet mount, with a similar specificity (97–100%) [2]. POC testing may be useful to increase laboratory confirmed trichomonas infection, especially in emergency room settings [20].

NAAT is similarly useful and provides the added benefit that it can be performed on vaginal or cervical secretions as well as urine. NAAT is the most sensitive test and provides high specificity as well (both 95–100%). This is the method recommended by the CDC in the 2015 STD Treatment Guidelines [23]. Routine Papanicolaou smear has poor sensitivity for *T. vaginalis*, but if the parasite is incidentally detected in this manner, the patient should be treated regardless of symptoms [2].

There are no clear screening guidelines for males. Males who are asymptomatic do not require screening. Even males with urethritis, however, are also infrequently diagnosed with *T. vaginalis*. NAAT is the only current FDA-approved test for detecting *T. vaginalis* infection in males. NAAT can be performed on urine samples with high sensitivity (100%) and specificity (88%) or urethral swabs (sensitivity 80%, specificity 93%) [18]. Urine collection may be easier to obtain for both clinicians and patients.

Treatment

Nitroimidazoles are the only antimicrobials found to be effective against *T. vaginalis*. The 2015 CDC guidelines recommend metronidazole or tinidazole 2 g as a one-time oral dose for all persons diagnosed with *T. vaginalis* infection. Sexual partners

Table 14.1 CDC 2015 trichomonas treatment guidelines [23]

Recommended treatment regimens
Metronidazole 2 g orally once OR
Tinidazole 2 g orally once
Alternate: Metronidazole 500 mg twice daily for 7 days

should be treated as well [8, 23]. Metronidazole has cure rates of 84–98% shown in randomized clinical trials, and tinidazole, which has higher drug concentrations in serum and in the genitourinary tract, has cure rates of 92–100% [11]. Intravaginal metronidazole gels have limited efficacy and should not be used as treatment [10].

Reinfection is common, often attributable to repeated intercourse with inadequately treated partner(s). However, if treatment failure (e.g., drug resistance) is suspected, treating with a longer course of the same medication is warranted. If metronidazole is ineffective, tinidazole 1 gram twice daily for 2 weeks *plus* tinidazole 500 mg vaginal tablets twice daily for 1 week has been shown to be effective. Tinidazole or metronidazole 2 g daily for 5 days can also be used in infections refractory to treatment [11, 23].

Antibiotic resistance to the class of nitroimidazoles has been detected, with more resistance to metronidazole than tinidazole. The prevalence of resistant trichomonas is unclear, especially for the adolescent and young adult population, as it is difficult to differentiate from reinfection. Because the nitroimidazoles are the only group of antibiotics with known effectivity, for a select group of women, other alternatives are necessary [11].

For persons with 5-nitroimidazole hypersensitivity, consultation with allergist is warranted with desensitization to metronidazole. Alternatives include intravaginal boric acid applied daily for 1–5 months, although data is limited, and this is not currently recommended by the CDC (Table 14.1) [14, 23].

Prevention

Condoms are the only effective preventive measure against *Trichomoniasis* [11]. Young women should be encouraged not to douche, as the resultant dysbiosis may increase the risk of acquiring vaginal infections such as *T. vaginalis* [21]. Ensuring partner treatment (and abstinence until both partners are treated) is also important to prevent reinfection.

Trichomonas and HIV

Trichomonas infection has been linked to both increased transmission and acquisition of HIV. The incidence of *T. vaginali*s infection is higher among people who have HIV relative to the general population. Treatment of *T. vaginali*s has also been linked to decreased genital tract viral shedding of HIV in females [11].

Females with active trichomoniasis are at higher risk for acquiring HIV. HIV-infected female patients with trichomoniasis are also at higher risk of developing pelvic inflammatory disease relative to those who are not infected with HIV. Females co-infected with HIV are also less likely to be cured of *Trichomoniasis* infection with single-dose metronidazole treatment (relative to females who are HIV-negative) and more often require a longer treatment course of metronidazole 500 mg twice daily for 1 week. Still, it is acceptable to initially attempt single-dose treatment but with a low threshold to prescribe the 7-day course if symptoms persist [11].

There is little data on trichomoniasis infection in males infected with HIV.

Trichomonas and Pregnancy

Trichomonas has been associated with increased risk for preterm delivery in women who are infected within the first 7 months of gestation. It is unclear whether treatment of pregnant women reduces this risk. Metronidazole as single-dose treatment is used if a pregnant woman is found to be infected, and as it is a pregnancy category B drug, it is not known to cause harm to the fetus. Of note, tinidazole is a pregnancy category C drug and should be avoided [11].

Currently, there is no standard recommendation for routine screening of pregnant women. Perinatal transmission is rare and there have been only 2–3 case reports published regarding this topic [11].

Special Populations

There are few studies which have looked at the risk of trichomoniasis infection in women who have sex with women (WSW), men who have sex men (MSM), and bisexual youth. One study indicates that African American women who have sex with women and men have higher rates of *Trichomoniasis* than African American WSW [15] though studies are limited.

MSM are infrequently infected with *Trichomoniasis*, and studies from an STI clinic confirm that trichomonas is rarely isolated from rectal specimens (0.3%) and does not cause symptoms of proctitis [5]. There are no known studies focused on trichomonas infection in transgender and gender non-binary persons.

Case Conclusion

Although she had a reassuring wet mount, with negative gonorrhea and chlamydia testing, suspicion for a sexually transmitted infection remained high given the change to her vaginal discharge. Knowing that the wet mount has a sensitivity of

only 51–65% (diagnosis of *Trichomoniasis*), the emergency room clinician sent NAAT from her urine which resulted positive. Though commonly described as causing a green, frothy discharge, this is seldom the case in actual clinical practice. She was called back within 24 hours and was treated with a single dose of metronidazole 2 g and asked to abstain from intercourse for 1 week. She was additionally provided with a metronidazole 2 g single dose for her partner. She was given anticipatory guidance for condom use, and her symptoms resolved after 1 week of treatment.

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Chapter 15
Mycoplasma genitalium

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Case Study
An 18-year-old heterosexual male presents with 3–4 days of penile discharge and dysuria. He reports multiple female sexual partners over the past month. A first-void urine specimen is collected and sent for for urine gonorrhea/chlamydia (GC/CT) nucleic acid amplification (NAAT) testing, and he is treated empirically with a single intramuscular dose of ceftriaxone (250 mg) and a seven-day course of doxycycline (100 mg orally twice daily). The urine GC/CT screen comes back negative. Two weeks after completion of his prescribed antibiotic course, the patient returns to the clinic with recurrent urethritis. He reports no new partners since the last encounter, and he states that he completed the course of doxycycline as directed. He reports that his urethritis symptoms improved while taking the antibiotics but recurred 2 days ago.

Discussion Questions:

1. What could be causing his current symptoms? What additional testing would you do?
2. What is the appropriate treatment for *Mycoplasma genitalium* urethritis?

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Introduction

Mycoplasma genitalium is an important cause of sexually transmitted infections (STIs) and is associated with urogenital infections among both men [1–4] and women [5–15]. It was first cultured in 1981 after being isolated from the urethral exudate of two men diagnosed with non-gonococcal urethritis (NGU) [16]. *M. genitalium* is a member of the Mycoplasmataceae family and Mollicutes class of bacteria [17]. Mycoplasmas are the smallest prokaryotes capable of self-replication and *M. genitalium*, with a genome of only 580 kilobases in size, is the smallest known free-living bacterium [11]. Due to its small genome, *M. genitalium* relies on a parasitic mode of life and is fastidious in its growth requirements [11]. Its lack of a cell wall prevents *M. genitalium* from identification by Gram stain, and its specific growth requirements make culturing *M. genitalium* difficult. Thus, despite the early recognition of *M. genitalium* in the 1980s, the study of the association between *M. genitalium* and disease syndromes could only be undertaken after the development of nucleic acid amplification tests (NAATs), namely polymerase chain reaction (PCR). *M. genitalium* is now recognized as being responsible for approximately 20–35% of non-chlamydial non-gonococcal urethritis (NCNGU) cases [4, 18]. Available data from studies of women suggest that *M. genitalium* also is associated with cervicitis [12, 14, 19, 20], endometritis [9], pelvic inflammatory disease (PID) [7], and tubal factor infertility [10].

Epidemiology

Prevalence

In the United States, the best prevalence estimates of *M. genitalium* among young adults (aged 18–27) comes from the National Longitudinal Study of Adolescent to Adult Health (Add Health) study. As of the 2007, the prevalence of *M. genitalium* in the Add Health cohort was approximately 1%, with the prevalence among men (1.1%) and women (0.8%) not differing significantly [21]. In context, *M. genitalium* infection among young adults was estimated to be more prevalent than *Neisseria gonorrhoeae* infection (0.4%), though less prevalent than *Chlamydia trachomatis* infection in that same group (4.2%) [21]. There are also racial/ethnic disparities; *M. genitalium* prevalence in this cohort was higher among Black (4.0%) and Latino (0.8%) young adults as compared to their white counterparts (0.4%) [21]. *M. genitalium* prevalence rates may be higher than the above estimates among youth (aged 14–17), with one study reporting a prevalence of 13.6% among a small sample of sexually active young women recruited from an urban primary care clinic who received quarterly PCR testing for *M. genitalium* regardless of symptomatology [22].

Globally, the prevalence estimates of *M. genitalium* in the general adult population range between 1% and 4% among men and 1–6.4% among women [23–25]. Higher prevalence rates of *M. genitalium* are reported among STI clinic attendees, with a wide range of estimates ranging from 4% to 38% [23, 26, 27]. Among asymptomatic men attending STD clinics, prevalence is 0.8–9.1% [4, 28–32] while the prevalence of *M. genitalium* among patients experiencing acute NCNGU is 18.4–45.5% [4, 28, 31, 33, 34].

Risk Factors

Factors associated with *M. genitalium* infection are similar to those for other STIs and include: higher number of sexual partners, recent sexual intercourse, co-infection with other STIs, having a partner with symptoms of an STI, younger age (<22 years old), younger age of sexual debut, smoking, and nonwhite race [12, 21, 22, 27, 35–39]. Furthermore, a positive relationship between sexual experience and *M. genitalium* infection was shown in the Add Health study that demonstrated that odds of *M. genitalium* infection increase by 10% for every additional sexual partner [21]. Interestingly, the study also found a strong association with ever having lived with a sexual partner and *M. genitalium* infection. As Manhart et al. suggest, this finding illustrates that transmission may require repeated exposure, and partners who cohabitate or have longer-term partnerships with an infected partner may be at greater risk [21].

Prevention

Currently, there is neither a vaccine against *M. genitalium* nor widespread screening in the general, asymptomatic population. Screening for *M. genitalium* Is hindered by the lack of a commercially available, FDA-cleared diagnostic test although many commercial laboratories and research hospitals use in-house PCR tests [40]. Where available, screening for *M. genitalium* should be considered for patients receiving STI testing as well as members of at-risk populations (e.g., more than one sexual partner, change of sexual partner, early sexual debut, younger age, and presenting with symptoms). Consistent condom use should be advised when engaging in both vaginal and anal intercourse to help prevent bacterial STIs, including *M. genitalium* [41]. Experimental data demonstrating condoms as effective barriers to *M. genitalium* is lacking; however, given that the approximate physical dimensions of *M. genitalium* (500 by 1000 nm, oblong) are considerably larger than those of HIV (100 nm, sphere), it is reasonable to assume that condoms would provide an effective barrier [42, 43].

Pathogenesis

M. genitalium has been isolated from multiple tissue sites, including synovial fluid, respiratory tract [44], urogenital tract [45, 46], and rectal specimens [47]. However, the urogenital tract is the preferred site of colonization [11] and the primary location to which clinical disease appears to be limited [48, 49]. *M. genitalium* attaches and adheres to the surface of epithelial cells utilizing a specialized terminal tip organelle before invading these cells [11]. Once inside epithelial cells, *M. genitalium* modulates the host immune system, including suppression and stimulation of lymphocytes and upregulation of cytokine expression, in an attempt to evade the host immune response [50]. While *M. genitalium* secretes mycoplasmal toxins and harmful metabolites like hydrogen peroxide, the majority of clinical disease associated with *M. genitalium* infection is believed to be due to the host's immune response to cell invasion [49]. *M. genitalium* can persist for months or years in infected individuals, as it can often be asymptomatic [51, 52].

Transmissibility

The sexual transmissibility of *M. genitalium* has been confirmed and is supported by epidemiologic and laboratory findings. As noted earlier, *M. genitalium* is detected more often among sexually active individuals with prevalence rising with an increasing number of sexual partners [3, 12, 13, 21, 22, 29, 38, 53, 54]. *M. genitalium* is more likely to be identified in samples taken from partners of *M. genitalium*-positive partners than *M. genitalium*-negative partners [3, 14, 22, 54, 55], and there is a high level of concordance in genotypes of *M. genitalium* identified between members of infected couples [56–58]. Additionally, *M. genitalium* has been shown in animal studies to hematogenously migrate from the primary site of colonization and invade other sites, such as joints [59]. While extra-genital infection has been documented among humans, including in the respiratory tract and synovial fluid [44], clinically significant disease appears limited to the genitourinary tract [48, 49].

Clinical Manifestations in Men

Urogenital Infection in Men

M. genitalium infection is strongly associated with acute non-gonococcal urethritis (NGU) in men [2–5, 13, 15, 28–33, 40, 60–72]. Among men attending STD clinics, nearly all (90%) of *M. genitalium*-infected men have been shown to have microscopic evidence of urethritis with approximately 75% reporting symptoms [39]. On exam, such urethral discharge is often grossly evident, however in some cases urethral stripping (applying gentle pressure along the penis from base to head) or

milking may be necessary for detection [69]. Clinically detectable discharge is more common with *M. genitalium* infection than with NGU of other etiologies [31, 39, 69, 73]. In addition to purulent or mucopurulent urethral discharge, the symptoms of urethritis caused by *M. genitalium* are similar to those reported in urethritis from other causes and include dysuria and urethral pruritus [40]. In *M. genitalium* infection, persistent or recurrent NGU has been documented following an acute attack [74]. Inflammation of the foreskin (posthitis) and the glans penis (balanitis), which often occur together, have also been associated with *M. genitalium* [75]. Additionally, some evidence suggests acute epididymitis may also be associated with *M. genitalium* infection [76].

Anorectal Infection Among MSM

Though under-studied, anorectal infection by *M. genitalium* is seen among patients with experience of receptive anal intercourse, including men who have sex with men (MSM) [47, 77–82]. Rectal infection in this population is rarely associated with symptoms [11, 77], with multiple studies reporting only asymptomatic rectal *M. genitalium* infection [77, 78]. However, *M. genitalium* can cause anorectal symptoms, as documented in a recent survey of 154 MSM experiencing symptoms of proctitis; 18 (11.7%) of these men were found to have anorectal *M. genitalium* infection [83]. When present, symptoms of rectal *M. genitalium* include proctitis (typically presenting with rectal pain or anal discharge) [83].

In one study of 1778 symptomatic and asymptomatic MSM screened for *M. genitalium* using both urogenital and anorectal samples, it was reported that 71.4% of those who tested positive did so only through an anorectal sample [80]. Unlike women, infection patterns among MSM with bacterial STIs often illustrate a single infection site rather than concurrent urogenital and anorectal disease (e.g., up to 91 and 70% for CT and NG, respectively) [84–91]. Given the high rates of asymptomatic anorectal *M. genitalium* infection, anorectal infections in MSM may represent an important reservoir for *M. genitalium*. Due to the association between *M. genitalium* infection and the increased risk of HIV infection [71, 92–98], regular screening of MSM (including rectal sampling) may be warranted.

Clinical Manifestations in Women

Urethritis

Relatively few studies documenting the role of *M. genitalium* among women (specifically cis-gender women) have been conducted [99]. Nonetheless, the evidence supporting an association between *M. genitalium* infection and urethritis among women is compelling [13, 14, 100, 101]. *M. genitalium* may also be implicated in a

"urethral syndrome" (frequency and dysuria in women with apparently sterile urine) or asymptomatic pyuria [11]. No data on *M. genitalium* infections specifically in transgender women are currently available.

Cervicitis

The available evidence suggests an association between *M. genitalium* infection and cervicitis [102]. Cervicitis due to *M. genitalium* infection is often asymptomatic [13, 14, 22, 103], with one study reporting only 23% of STD clinic attendees diagnosed with *M. genitalium*-associated cervicitis as symptomatic [14]. Cervicitis symptoms associated with *M. genitalium* infection tend to be nonspecific with vaginal discharge reported most commonly [20, 22, 104] as well as vaginal itching, dysuria, and pelvic discomfort [103]. Physical examination findings associated with *M. genitalium* infection include cervical inflammation, purulent or mucopurulent cervical discharge, cervical friability, and an elevated polymorphonuclear leukocyte (PMN) count on a cervical fluid Gram stain or vaginal smear [5, 13, 14, 100, 101].

Pelvic Inflammatory Disease (PID)

Relatively sparse data are available on pathogenesis of *M. genitalium*-associated PID, and suggest that *M. genitalium* in the cervix invades the upper genital tract and causes PID following sexual acquisition [7, 9, 53, 105–107]. Women presenting with cervical *M. genitalium* infection are estimated to be more than twice as likely to also have PID than those without *M. genitalium* infection [102]. Symptoms of PID associated with *M. genitalium* infection include mild to severe pelvic pain, abdominal pain, abnormal vaginal discharge, and/or bleeding, and are indistinguishable from symptoms of PID due to *Chlamydia trachomatis* [108].

Anorectal Infection

Although few studies have investigated the role of *M. genitalium*-related anorectal disease in women, *M. genitalium* has been detected in a large proportion of rectal samples among randomly screened women with and without prior anal sex experience (ranging from 4.3% to 8.1%) [109, 110]. While several studies report a high level of association between anorectal *M. genitalium* infection and concurrent urogenital infection, as is often the case with bacterial STIs among women, discordance is also seen [99, 109, 110]. As with anorectal infection among men, anorectal *M. genitalium* infection among women is typically not associated with symptoms

and as such may represent an important reservoir potentially facilitating onward transmission [11, 77].

Adverse Pregnancy Outcomes and Infertility

While more information is needed on the effects of *M. genitalium* in pregnancy, available evidence suggests that *M. genitalium* may be associated with adverse pregnancy outcomes, such as preterm birth and spontaneous abortion [102]. Regarding infertility, it remains unknown if *M. genitalium* is specifically associated with tubal factor infertility, as the few studies on this issue have yielded indirect and conflicting results [11, 27]. One seroepidemiological study found no association between presence of *M. genitalium* antibody and tubal factor infertility, while two such studies reported higher rates of *M. genitalium* antibodies among women with tubal factor infertility (17–22%) compared to women with normal tubes (4–6%) [11, 27].

M. genitalium and HIV

It is well documented that concurrent STIs increase both the risk of acquiring and transmitting HIV; this effect appears to apply for *M. genitalium* as well [111]. Prevalence of *M. genitalium* among persons living with HIV is frequently reported as significantly higher than HIV-uninfected individuals with estimates ranging from 3.1% to 47.5% [71, 83, 98]. *M. genitalium* has been associated with an increased risk of HIV infection in several studies [71, 92–98] with one study showing *M. genitalium* to be more common among individuals who subsequently became infected with HIV compared to matched controls (14.8 compared to 6.5%) [97]. A high burden of *M. genitalium* among HIV-infected women has also been associated with increased HIV-1 DNA shedding compared to HIV-infected women not co-infected with *M. genitalium* [112].

Diagnosis

M. genitalium is not visible on Gram stain due to its lack of cell wall, and its fastidious growth requirements make culture difficult [11, 27]. As such, the only current diagnostic test available for *M. genitalium* is nucleic acid amplification testing (NAAT) using PCR. *M. genitalium* detection via PCR was first described in the early 1990s [113], and the first real-time PCR assay was developed a decade later [114]. Unfortunately, appropriate testing for *M. genitalium* may not be available in all clinical settings and is unlikely to be included in routine STI screen-

ings. Despite the lack of an FDA-cleared screening assay for *M. genitalium,* clinicians may consider adding *M. genitalium* to routine STI screening by utilizing in-house PCR assays available through commercial laboratories (i.e. Quest Diagnostics).

Specimens appropriate for the detection for *M. genitalium* include urine, urethral swab, rectal swab, endocervical swab, and endometrial biopsy [27]. Note that *M. genitalium* infection of the pharynx has not been demonstrated and screening of such samples for *M. genitalium* is not currently recommended [11, 27]. When collecting urine samples, the first 10 mL of the initial stream of urine collected should be collected without pre-cleaning the genital areas (first-void urine). Ideally, the patient should not have voided in the 2 hours prior to specimen collection. Among men, first-void urine appears to be more sensitive in detecting *M. genitalium* (96.6%) than urethral smear specimens (82.5%) [115, 116]. Among women, the superior sensitivity of *M. genitalium* detection via vaginal swabs has been repeatedly demonstrated [37, 110, 117–119]. One study estimates the relative sensitivity of *M. genitalium* detection via vaginal swab as 86% versus 61% for first-void urine specimens [110].

Treatment

M. genitalium is generally susceptible to tetracyclines, fluoroquinolones, macrolides, and clindamycin and is resistant to those antimicrobials which act on bacterial cell wall components (e.g. penicillins), due to its lack of a cell wall [11]. Azithromycin demonstrates greater than 100-fold more activity in vitro against *M. genitalium* than any of the tetracyclines or quinolones [120–122]. Superior cure rates from a single 1 g dose of azithromycin (compared with doxycycline 100 mg administered twice daily for 7 days) have been documented in urethritis [21, 117, 123, 124], cervicitis, and PID [125, 126]. The pooled cure rate reported for *M. genitalium*-infected men experiencing urethritis treated with a single 1 g dose of azithromycin is 80%, compared to a pooled cure rate of 42% in those treated with doxycycline (100 mg dose orally twice daily for 7 days) [123]. Among women infected with *M. genitalium* and treated with a single 1 g dose of azithromycin, the pooled cure rate is 87%, superior to cure rates reported with doxycycline treatment (100 mg dose twice daily for 7 days) of between 37% and 48% [125, 127, 128]. Unfortunately, *M. genitalium* resistance to azithromycin is well described, with reports ranging from 13% to 40% of isolated samples [129–131]. While some studies have shown slightly higher cure rates after a five-day course of azithromycin (e.g., 96 versus 85%) [125, 126], the single 1 g dose has the potential for directly observed therapy at point of care. Among patients who fail treatment with a single 1 g dose of azithromycin, treatment with moxifloxacin has been shown to be effective [123, 132, 133] with one study reporting a superior cure rate with moxifloxacin (400 mg dose daily for 7 days) (88%) than with a follow-up five-day course of azithromycin (34%) in this population [43, 133]. Given the sexual transmissibility of *M. genitalium*, sexual partners of

patients with confirmed *M. genitalium* infection should be contacted for screening and potentially empirical treatment.

Case Conclusion

A first-void urine specimen is collected and sent for PCR screening which identified *Mycoplasma genitalium* infection. The patient was treated with a single 1-g oral dose of azithromycin in the office. The patient is asked to return in 3 weeks to confirm successful treatment and offered partner notification services to connect recent partners to care for testing and treatment. At confirmatory screening, patient reports resolution of symptoms and urine screen for *M. genitalium* returned negative.

Summary

- In the United States, the prevalence of *M. genitalium* infection among young adults is approximately 1%, which is more prevalent than *Neisseria gonorrhoeae* (0.4%) and less prevalent than *Chlamydia trachomatis* infection (4.2%).
- Among men, *M. genitalium* is a common cause of urethritis and is associated with symptoms such as purulent or mucopurulent urethral discharge, dysuria, and urethral pruritus. Women with cervicitis associated with *M. genitalium* are more often asymptomatic. When present, cervicitis symptoms are frequently nonspecific with vaginal discharge, vaginal itching, dysuria, and pelvic discomfort reported. Among both men and women, virtually no association has been demonstrated between rectal *M. genitalium* infections and anorectal signs and symptoms.
- *M. genitalium* infection is diagnosed via nucleic acid amplification testing (NAATs) using PCR from a swab (urogenital, anorectal) or urine sample, although many clinical sites are unable to perform this test.
- Confirmed *M. genitalium* should be treated with a single 1-g dose of azithromycin. Treatment failures should be treated with moxifloxacin.

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Chapter 16
Herpes Simplex Virus

Nathalie H. Duroseau and Robyn R. Miller

Case Study
A 16-year-old female patient presents for an acute care visit, complaining of multiple painful vaginal lesions that started about 5 days ago. Initially, she noted a single painful welt-like lesion while urinating, and tried placing A&D ointment on it (thinking the lesion may have been an ingrown hair). Over the course of several days, multiple similar lesions appeared and her surrounding vaginal area became excruciating painful to even light touch. She is unable to shower or urinate without pain. She denies dysuria, abnormal bleeding or vaginal discharge. She has been sexually active with 1 male partner for the past 2 months. Her most recent sexual activity was approximately 7 days ago. She uses condoms 50% of the time, and nexplanon for contraception. Her last menstrual period was 2 weeks ago, and her periods are regular. She was last tested for STIs 9 months ago.

On exam, she is afebrile and her vital signs are within normal limits. Physical examination is notable for eight small, superficial ulcers, each less than 1 cm in size. Four of the ulcers are located on the internal aspect of the labia majora, and the other four are on the internal aspect of the labia minora.

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Her physician performs a vaginal exam and tests for candidiasis, bacterial vaginosis, chlamydia, gonorrhea, and trichomoniasis. She also collects a swab to test for Herpes Simplex Virus (HSV)-1 and HSV-2 PCR. The decision is made to provide empiric treatment for HSV while test results are pending. She is prescribed valacyclovir 1 g tablet for 10 days and lidocaine 5% ointment to use on her vaginal area 4 times daily and prior to urination. One week later, her vaginosis swab returned positive for Candida and BV, and her HSV PCR was positive for HSV 2.

Questions:

1. What are the signs and symptoms of a HSV outbreak?
2. What, if any, are clinically significant differences between HSV-1 and HSV-2 infection?
3. How should clinicians decide between episodic vs long-term suppressive antiviral treatment?
4. What anticipatory guidance should be given regarding asymptomatic shedding and viral transmission?

Epidemiology

Genital herpes is caused by herpes simplex virus type 1 (HSV-1) or herpes simplex type 2 (HSV-2). It is one of the most common sexually transmitted diseases globally, and is associated with significant physical and psychological morbidity. Spread by direct genital-genital transmission (usually HSV-2) or oral-genital transmission (usually HSV-1), genital herpes is commonly diagnosed in sexually experienced adolescents and young adults. However, upwards of 90% of infected individuals are unaware they are infected. HSV-1 is nearly ubiquitous in the general population, with an estimated seroprevalence of greater than 90% in developed nations. HSV-2 is estimated to infect over 500 million people worldwide, with approximately 23 million new infections each year. The virus is transmitted through periodic viral shedding in both symptomatic and asymptomatic individuals. Once infected, HSV persists indefinitely in a dormant state within sensory nerve ganglia until it is reactivated [1–4].

HSV-1 is primarily associated with oral, pharyngeal, facial, ocular, and central nervous system infections and largely transmitted by oral secretions and non-genital contact. HSV-1 is traditionally thought to be transmitted during early childhood, predominantly affecting the body above the waist by causing recurrent painful orolabial and facial lesions. HSV-1 is also responsible for common pediatric infections including herpetic gingivostomatitis, eczema herpeticum, herpes gladiatorum, and herpetic whitlow [5, 6]. Serious complications of HSV-1 include devastating neonatal diseases such as ocular herpes (one of the leading cause of neonatal corneal blindness) and meningoencephalitis, which can be transmitted intrapartum and in the postpartum period via contact with infected healthcare workers or family

members. HSV-1 can remain viable on the skin, clothing, or plastic for brief periods, facilitating transmission through close nonsexual contact, such as kissing on the cheeks or sharing common utensils. Both HSV-1 and HSV-2 can cause genital herpes, however HSV-1 infections are associated with fewer outbreaks and less viral shedding compared to HSV-2 infections [4, 5, 7, 8].

Although there is ample data regarding the prevalence and incidence of HSV-2 infections, there is a relative paucity of data on the global burden of HSV-1. In 2012, it was estimated that 3.7 billion people globally aged 0–49 years were infected with HSV-1, and that an estimated 140 million people were infected with *genital* HSV-1. In the US, the rates of HSV-1 infection are strongly associated with race and socioeconomic status with 35% of 5-year-old African American children demonstrating HSV-1 antibodies virus compared to 18% of white children. In addition, HSV-1 affects nearly 33% of children by age 5 in lower socioeconomic populations and extends to nearly 70–80% by late puberty [5–9].

Over the past decade the epidemiology of HSV-1 genital infections has dramatically shifted. Although the overall HSV-1 seroprevalence in the US has decreased, HSV-1 is now emerging as a principal causative agent of genital herpes in the US and other developed nations. The proportion of genital herpes caused by HSV-1 has especially increased among college-aged individuals. Data obtained from recent HSV vaccination trials in the US indicate that nearly 60% of incident genital herpes infections were attributable to HSV-1 and that most women acquired HSV-1 but not HSV-2 infections before 18 years of age [4, 8]. There are several factors that have been suggested to explain the higher proportion of genital HSV-1 infections in college students including changes in sexual practice and delayed acquisition of oral HSV-1. Adolescents and young adults are more likely to engage in oral sex, which is viewed as safer than vaginal intercourse (as a means of averting pregnancy), thus increasing the frequency of genital-oral contact with a partner who may have oral labial herpes [8, 10–14]. In addition, increased use of condoms for intercourse has reduced exposure to HSV-2 resulting in lower relative incidence rates in comparison to HSV-1. Improved socioeconomic status and hygiene in society at large have resulted in delay or lack of acquisition of oral HSV-1 infection early in life, leaving older children and adolescents more susceptive to genitally acquired HSV-1 infections as they become sexually active. These trends suggests that oral HSV-1 infections may confer partial protection against subsequent genital HSV-1 exposure; even if acquired, the infection may be less severe or subclinical. This concept is further supported by the low rate of clinical HSV-1 associated genital herpes among US nonwhite minorities, who exhibit a higher rate of oral HSV-1 acquisition during childhood as discussed above. In addition, it appears that those who acquire HSV-2 infection without a previous HSV-1 infection have been shown to have more severe symptoms of HSV-2 infection because antibodies to HSV-1 attenuates the severity of HSV-2 disease but does not prevent infection with HSV-2 [15].

HSV-2 prevalence and epidemiology has been more frequently described in the literature compared with HSV-1. Rates of HSV-2 infection are lower than HSV-1 given that HSV-2 is nearly exclusively transmitted by sexual contact and thus majority of infections occur after the start of puberty with the initiation of sexual

intercourse [2, 9]. HSV-2 seroprevalence rates vary by race, age, sex, number of lifetime sexual partners, and socioeconomic status. The prevalence of HSV-2 rises in adolescence and increases through young adulthood, eventually leveling off around 40 years of age. In the United States, the mean age at presentation with new HSV genital infection is 24 years of age. Similar to HSV-1, HSV-2 infection rates also vary between racial groups. African-Americans have been found to have 2.6 times higher rates of HSV-2 infection compared to Hispanics, and 5.5 times higher rates than Whites [1, 12]. Women have a greater risk of HSV-2 acquisition than men, reflecting both increased biologic susceptibility and relationships between younger women and older men (who are more likely to be HSV-2 seropositive). It has been hypothesized that men have more asymptomatic genital HSV-2 infections than women, which could lead to higher rates of viral transmission from men to women [4, 8, 13, 14]. The combination of both gender and race effects results in a disproportionate burden of HSV-2 infection affecting African-American women. For example, for white women, the risk of HSV-2 increases from about 18% among those with 2–4 lifetime partners to 35% for those with 10–49 lifetime partners. In contrast, for African-American women the risk increases steeply even with fewer partners, exceeding 60% for women with more than 4 lifetime partners. For white men, the risk is ∼10% among those who report 2–9 lifetime partners, and reaches 40% in those with >50 lifetime partners. Among African-American men, the risk rises from 35% in those with 2–4 lifetime partners to ∼ 50% in those reporting >50 lifetime partners [13, 14].

Virology

Herpes Simplex virus type 1 and type 2 belong to the subfamily Alphaherpesviridae within the Herpesviridae family of viruses. This subfamily also includes varicella zoster virus, cytomegalovirus, Epstein-Barr virus, human herpesvirus 6 and 7, and Kaposi's sarcoma-associated herpesvirus (type 8) [2, 5, 12]. HSV-1 and HSV-2 are both double stranded DNA viruses composed of 4 parts: a dense core containing viral DNA, an icosapentahedral capsid, a layer of proteins surrounding the capsid, and an envelope. To initiate infection, HSV attaches to at least three different classes of cell-surface receptors and fuses its envelope with the plasma membrane. The capsid, minus its envelope, is transported to the nuclear pore, through which it releases viral DNA into the nucleus. HSV replicates by three rounds of transcription that yield: α (immediate early) proteins that mainly regulate viral replication; β (early) proteins that synthesize and package DNA; and γ (late) proteins, most of which are virion proteins. HSV viral replication in the cells is a cytolytic process that causes irreversible cell damage. Virions within epithelial cells cause the cells' plasma membranes to fuse and form multinucleated giant cells. Ultimately, the multinucleated giant cells lyse and form characteristic fluid-filled blisters comprised of cell debris, inflammatory cells, and more viral progeny between the epidermis and dermal layers of skin. As the skin heals, the vesicles becomes pustular and crust

over. Mucous membrane vesicles typically do not scab or crust over, but are replaced by shallow ulcers instead [5, 16].

HSV-1 and HSV-2 exhibit several unique biologic properties that influence pathogenesis and subsequent human disease: "*neuroinvasiveness* – the ability to invade the brain; *neurotoxicity* - the ability to multiply and destroy the brain; and *latency* – the ability to remain in non-replicating form in neurons of the dorsal root ganglia" [17]. Once HSV has penetrated the dermis, the DNA-containing nucleocapsid travels from the end of the peripheral sensory nerves innervating infected cells and is transported by retrograde axonal transport to the sensory root ganglia. Viral replication continues to occur in a small fraction of neurons that ultimately die, and the majority of the active virus is maintained in a latent state. Once located in the dorsal root ganglia, the virus can remain latent for the life of the host. There are three phases of latency – *establishment*, *maintenance*, and *reactivation*. *Establishment* occurs during the period following primary infection where the normal progression of HSV and cell death is arrested in the neurons destined to become latently infected. The *maintenance* phase is characterized by the lifelong retention of the HSV genome in a silent state by repression of all viral lytic genes. The last phase, the *reactivation* phase, is characterized by the silent genome responding to cellular signals that provoke the resumption of viral gene expression and ultimately the development of vesicles and ulcerations [2, 17, 18].

Clinical Manifestations

Primary Infection

HSV must come in contact with mucosal surfaces or abraded skin to initiate infection. It subsequently replicates locally in the keratinocytes of skin, epithelial cells of mucous membranes, and regional lymph nodes [2]. The average incubation period is estimated to be 4 days, but ranges from 2 to 10 days. In its most classic presentation, primary HSV infection begins with a visible outbreak of macules and papules that progress to vesicles, pustules and ulcers [2, 16]. The lesions typically appear 4–7 days after sexual exposure and can last upwards of 3 weeks. Lesions on the external genitalia are typically bilateral and clustered, and can also be found in the perineum, buttocks, or inner upper thighs. Primary genital lesions can also be associated with pain, itching, burning, dysuria, cervicitis, proctitis (in individuals who engage in receptive anal intercourse), and pharyngitis (in cases of oral acquisition). A brief viremia can lead to a prodrome characterized by malaise, fever, and localized adenopathy. Complications such as aseptic meningitis, urinary retention, mucocutaneous lesions beyond the genital area, and visceral dissemination are rare, but occur more commonly in women than men [3, 16, 18, 19]. Labial adhesions may occur as a severe complication of primary genital herpes, particularly in young adolescent women – this can often occur due to prolonged

delay in diagnosis and therapy given young age and accompanying low index of suspicion. However, the majority of individuals with primary genital herpes are asymptomatic. It is estimated that upwards of 90% of infected individuals have a clinically unapparent course of primary HSV infection [5, 6, 16]. Individuals who are considered to have an "initial nonprimary" genital HSV infection (i.e. those who have previously been infected with one strain HSV-1 or HSV-2 and developed antibodies and then acquire an additional strain infection) are less likely to have systemic symptoms during their initial infection due to the cross-reactivity of HSV-1 and HSV-2 antibodies. Initial nonprimary infections are also associated with lower rates of complications, shorter duration of disease, shorter duration of viral shedding, and fewer lesions [2, 5, 16, 20, 21].

Recurrent Genital Herpes

After the onset of primary infection, both HSV-1 and HSV-2 migrate via retrograde axonal transport to sensory nerve ganglions innervating the site of infection and establish latency. From there, the virus can be reactivated and cause recurrent skin and mucosal infections. Multiple factors can trigger a reactivation. For example, emotional stress, menses, sexual intercourse, and immunocompromised states have been some of the factors implicated in precipitating recurrences [22, 23]. Recurrences can be either symptomatic or asymptomatic. The more severe the primary infection (as reflected by the size, number, and extent of lesions), the more likely it is that recurrences will ensue [2, 5, 6]. Recurrent infections can occur in upwards of 40% of individuals with latent HSV-1 or HSV-2. In recurrences (as opposed to primary presentations), lesions are usually unilateral and resolve within 5–10 days. Recurrent lesions can be atypical, sometimes appearing as furuncles, patchy erythema, linear fissures or excoriations. On the basis of clinical examination, it is often impossible to determine definitively whether a first symptomatic episode of genital herpes is initial or recurrent disease, although the presence of a prodrome suggests a recurrence. Infection with HSV-1 generally occurs in the oropharyngeal mucosa, and typically resides in the trigeminal ganglion resulting in recurrences of HSV lesions around the oral cavity. The outer edge of the vermilion border is the most common site of reactivation; on average three to five lesions are present. Recurrences of HSV-1 in the genital tract are uncommon. Oral HSV-2 shedding is nearly always asymptomatic, and often conconcurrent with genital HSV-2 shedding. HSV-2 recurrences of the mouth are uncommon. The prodome associated with recurrent genital herpes can be variable and range from mild tingling occurring 30 minutes to 2 days prior to eruption to dramatic paresthesia and pain in the lumbosacral area lasting as long as 5 days prior to eruption. Recurrent genital infection in males can appear as 3–5 vesicles on the shaft of the penis, or ulcerating-vesicle genital lesions or vulvar irritation in women lasting 8–10 days. About 90% of individuals with clinically apparent HSV-2 genital herpes will have at least 1 recurrence, 38% have 6 or more, and 20% have 10 or more recurrences [5, 20].

Viral Shedding

HSV can be transmitted to sexual partners in the presence or absence of symptoms. In fact, asymptomatic viral shedding accounts for a significant majority of HSV-2 transmission. Symptomless shedding occurs in approximately 3–5% of women previously infected with HSV-2 [4, 21]. Transient episodes (often <24 hours) of asymptomatic shedding of infectious virus from multiple genital sites have been detected with the use of PCR in 80–90% of HSV-2–seropositive persons. For example, in one study 83 percent of subjects who were HSV-2–seropositive but who reported having no history of genital lesions had genital shedding of HSV at some point during a 36-month follow-up period. Additional studies have also indicated that shedding occurs at unpredictable intervals and during 10–20% of days per month for some subjects [24]. In any given sexual encounter, the risk of transmission to a susceptible partner is higher when symptomatic genital lesions are present (owing to higher quantities of HSV present with active lesions) than when viral shedding is asymptomatic. However, the high frequency of asymptomatic shedding makes it the leading source of new cases [2, 7, 25–27].

HSV Laboratory Diagnosis

Laboratory confirmation of clinical presentations of HSV is highly recommended for a variety of reasons. Laboratory testing can help narrow the differential diagnosis in cases of variable presentations of genital herpes and differentiate from other ulcerative STIs or ulcerative dermatoses, such as Crohn's or Bechet syndrome. Identification of the type of HSV can help clinicians provide education to their patients regarding natural progression, prognosis, and guidance regarding the multiple complex social and psychosexual implications associated with genital HSV. In addition, laboratory testing helps to determine the need for antiviral treatment courses for infected individuals, their sexual partners, and future offspring. It may also prevent unneeded antiviral therapy in patients with atypical presentations and negative testing, and support continued investigation for alternative diagnoses [28, 29]. Genital HSV can be confirmed with a variety of techniques including: viral culture, polymerase chain reaction (PCR), direct fluorescence antibody, cytological smear, and type-specific serologic tests (TSS). The choice of test varies with the clinical presentation and availability in a given clinic/laboratory setting. Overall, PCR has higher sensitivity compared to viral cultures and TSS, and should be the test of choice for symptomatic cases. Cytological detection of cellular changes associated with HSV infection (i.e., Tzanck preparation) is an insensitive and nonspecific method of diagnosing genital lesions and should not be relied on. Tzanck smears should be only be considered when an urgent result is needed and no alternative test is immediately available. Although a positive result is more useful, a negative Tzanck smear would still require follow-up testing of with a more sensitive test.

Direct immunofluorescent (IF) assays using fluorescein-labeled monoclonal antibodies also lack sensitivity in comparison to the other methods. Of note, other causes of genital ulcers such as *Treponema pallidum* and *Haemophilus ducreyi* should also be considered, and testing should be obtained for patients presenting with genital lesions in areas where there is epidemiological predominance. Finally, due to the intermittent nature of viral shedding, failure to detect HSV by culture or PCR does not indicate an absence of HSV infection, especially in the absence of active lesions [30–32].

Viral Cultures

Once considered the gold standard for HSV, viral isolation in tissue culture should be reserved for patients with active primary lesions. In order to perform a viral culture, the clinician must obtain a collection of fluid from the base of an intact vesicle by unroofing the vesicle with vigorous swabbing with either a small cotton or nylon tipped swab or a sterile needle and transfer it to a viral media. There is anecdotal evidence that nylon swabs are preferred –fibers can act like a soft brush, allowing for improved collection and release from samples. Calcium alginate swabs are toxic to HSV and should not be used for virus isolation in cell culture. HSV is sensitive to temperature and to moisture – therefore, it is imperative that the sample be transported on ice and grown in an appropriate cell culture such as Eagle's medium. Samples can be stored at +4 °C and frozen until molecular analysis for up to 48 hours, and should not be kept for more than 4 hours at room temperature. If there is an expected delay of more than 48 hours between collection and culture, the specimens should be frozen at −80 °C until inoculation. Once placed in media, HSV forms irreversible, characteristic changes inside the cells, including ballooning degeneration, the formation of multinucleated giant cells, and is ultimate typed by antibody staining. Viral culture is relatively slow, taking an average of 5 days to achieve maximum cytopathological changes. The sensitivity for viral cultures dramatically fall, by as much as 50%, for healing, dried, crusted, or aged lesions and is overall low in those who have recurrent infections rather than primary infections. Therefore, negative viral cultures do not necessarily rule out cases of genital herpes (depending on the time frame) and offer little information in the setting of asymptomatic recurrences with subclinical shedding [31, 32].

PCR

Real time PCR has emerged as the most sensitive and reliable method to confirm HSV infection in clinical specimens obtained from genital ulcers and mucocutaneous sites. PCR has been FDA approved since 2011. In comparison to viral cultures, PCR assay is rapid (takes about 1 day for results to be reported), type-specific, and

cost competitive. Molecular testing will also confirm viral shedding whether or not lesions are present. The sensitivity of PCR is superior to viral cultures and approaches 100% when assays are performed on vesicles or wet ulcers. Though imperfect, sensitivity and is still considerably higher than viral cultures when testing older, dry, or crusting lesions. In one study, among women who underwent daily sampling of genital lesions, HSV DNA was detected in ulcerative lesions on 15 of 17 days compared to only 3 of 17 days by viral culture. PCR is also particularly useful for the detection of asymptomatic HSV shedding, and has also been used in clinical studies to evaluate the risk of transmission in discordant couples and the effectiveness of suppression with antiviral therapy. Of note, there is a theoretical risk of false-positive results occurring due to sample contamination before amplification. Samples giving discordant results (e.g., positive by PCR and negative on culture) are usually confirmed by a second PCR directed to a different gene to ensure assay specificity [29–35].

Serology

The routine use of HSV TSS remains controversial, and is generally discouraged. Currently, HSV TSS is only indicated for targeted use in specific diagnostic situations and select patient populations. For example, serologic testing may be considered in cases where there are no lesions, healing lesions in the setting of negative virus culture or PCR, recurrent HSV-2 symptoms with atypical presentations, negative viral culture or PCR, and the diagnosis remains unclear. HSV-2 TSS can be beneficial for HIV+ patients, discordant couples, women who develop their first clinical episode of genital herpes during pregnancy, asymptomatic pregnant women whose partners have a history of genital herpes or HIV infection, and women contemplating pregnancy or considering sexual partnership with those with a history of genital herpes [32–35].

It is important to consider the numerous ethical issues regarding the ethics of HSV serological testing, including poor positive predictive value in populations with low HSV prevalence; psychological damage from testing positive for HSV; low utility of testing people who have no symptoms; and cost-effectiveness. Since genital ulcers have many possible etiologies, a positive HSV IgG antibody serology cannot be used for diagnosis of an active genital ulcer without further diagnostic evaluation. In contrast, a positive viral culture or PCR for HSV in a HSV seronegative patient is strong evidence of primary infection. False-negative results may also occur in new infections because of the delayed appearance of HSV IgG. False-negative results should be verified clinically or a repeat serology performed at a later date if seroconversion is suspected. Lastly, it is unclear if there is a major public health benefit in testing individuals with no symptoms. Currently, physicians would be unlikely to prescribe suppressive antivirals to such individuals, and there is no evidence that diagnosing genital herpes asymptomatic individuals would change their sexual behavior to block transmission. In summary, without knowing

the benefits of testing, the risk of shaming and stigmatizing people outweighs the potential benefits [22, 35–38].

Additionally, HSV TSS is generally not useful for distinguishing between HSV-1 and HSV-2 infection. The two viruses share greater than 70% identity at the level of their genome sequence. Of over 80 proteins encoded by their respective genomes, only gG (designated as gG-1 and gG-2 for HSV-1 and HSV-2, respectively) has proven to be clinically useful to differentiate antibody response between these viruses. IgM testing for HSV-1 or HSV-2 is not useful, because IgM tests are not type-specific and might be positive during recurrent genital or oral episodes of herpes. The appeal of type-specific serology using surface glycoproteins is that it should theoretically allow the clinician to determine if the patient is at risk of acquisition or has evidence of prior infection with either subtype. However, TSS remains problematic because while HSV-2 TSS reactivity is generally indicative of genital herpes, HSV-1 TSS is not specific to an anatomical location. Reactive HSV-1 serology may indicate either oral or genital herpes. More importantly, the extremely high prevalence of HSV-1 in the general population further limits the interpretation of a positive result. Several commercially available tests have shown a high level of cross-reactivity in the range of 47–82% with HSV-1 and HSV-2, along with an overall relatively low specificity. For these reasons, most infectious diseases specialists and laboratory professionals argue that HSV serology is not clinically useful and, thus, should not be routinely offered [7, 15, 39, 40].

Treatment

A primary episode of HSV should be treated with oral antiviral therapy to prevent prolonged clinical illness with severe genital ulcerations. Prompt initiation of antiviral therapy within 72 hours of lesion appearance is recommended in order to decrease lesion duration, severity of illness, and development of complications. Antiviral therapy is also recommended for patients who present after the initial 72-hour time frame with either continued development of new lesions or significant pain. Acyclovir, valacyclovir, and famciclovir are effective therapies for genital herpes caused by HSV-1 or HSV-2 with excellent safety profiles and rare adverse reactions. The efficacy among these antivirals is generally similar, and selection of a specific drug is based on the convenience of administration, cost, and clinician preference. For example, valacyclovir is the most convenient medication regimen at a dose of 1 g orally twice daily for 7–10 days for first time clinical episodes, in comparison to famciclovir and acyclovir which are administered 3–5 times daily. However, valacyclovir is on average more expensive than the two other options. Analgesics, such as 2% lidocaine jelly and warm sitz baths can be added to treatment regimens to provide symptomatic relief. Patients can also consider diluting urine with running water or using Vaseline as a skin barrier in order to prevent burning and irritation that can occur when urinating (and subsequent urinary retention). Vaseline is a particularly effective measure when patients have to use public

or school restrooms, making diluting urine with water less feasible. Topical antiviral therapy is only marginally effective and is not generally recommended. Parenteral treatment should be reserved for those with severe genital disease and/or complications such as CNS disease, end organ damage and disseminated HSV. For those individuals, the CDC recommends starting intravenous acyclovir (5–10 mg/kg, every 8 hours) until clinical improvement is documented, followed by transition to oral antiviral therapy and complete at least 10 days of therapy [2, 7, 15, 23, 41].

Providers should consider frequency and severity of outbreaks, as well as patient preference when deciding between episodic or suppressive treatment. The presence of severe psychological stress related to HSV outbreaks may favor suppressive therapy regardless of outbreak frequency; while the lower cost and convenience of short-term therapy may favor episodic treatment for some patients. Acyclovir, valacyclovir, and famciclovir are used for both symptomatic recurrences and suppressive therapy. Episodic treatment should be considered for individuals with fewer than six symptomatic recurrences annually to decrease the duration of signs and symptoms associated with HSV infection and the duration of viral shedding. Patients should be counseled and supplied with a prescription in order to self-administer therapy at the first sign of prodromal symptoms (tingling, paresthesia, and pruritus). Initiation of therapy within the first 24 hours of symptoms has been demonstrated to lead to faster resolution of recurrent cutaneous lesions and clinical symptoms. The duration of therapy can range from 1 to 5 days for an acute recurrence [41–44].

Patients who experience six or more symptomatic episodes annually should be started on suppressive therapy or long-term daily drug administration to reduce the frequency of symptomatic recurrences. Suppressive therapy, in particular with valacyclovir, is recommended for discordant couples because it can significantly reduce the frequency of asymptomatic shedding of HSV-2 and the risk of transmission to an HSV-2 negative partner.

Suppressive therapy can also be offered to those who experience significant anxiety or distress related to their recurrences. In addition, randomized, double blinded clinical trials have indicated that valacyclovir is superior to other agents for patients who have greater than 10 recurrences annually. There is limited data on the length of time that suppressive therapy can be used. However, some studies have shown suppressive therapies can safely be given for upwards of 6 years. The necessity of continued treatment should be evaluated annually as the natural history of HSV is for occurrences to decrease over time with or without treatment [42, 43, 45, 46].

Prevention

Prevention of genital HSV should primarily focus on decreasing overall HSV transmission and decreasing the morbidity and psychological stress for those already infected. Education and counseling is the cornerstone of prevention. Although the

prevalence of genital HSV is high, there is a significant number of young people in the US who are unaware of their susceptibility. A significant amount of attention is focused on the negative physical and psychological impact of HSV infection. Young adults may inaccurately believe that they have limited control over infection and that a diagnosis may have a more severe impact on their mental health and intimate relationships. Others may miss opportunities for testing or intervention due to the belief that all HSV infections are symptomatic and that without an active lesion they are not infectious. Clinicians should not underestimate the preconceived notions that an individual may have regarding a HSV diagnosis and address issues that arise such as anger, disbelief, low self-esteem, and fear of rejection by present and future sexual partners. Clinicians should consider integrating into their practice methods for stress reduction such as short-term cognitive behavioral therapy, stress management, and relaxation techniques for those who experience significant distress regarding their recent diagnosis or recurrent genital ulcers. There is evidence that incorporating some of these methods has been found to reduce the frequency of genital herpes recurrences. For example, short-term, structured, symptom focused group therapy has been found to be helpful for individuals with genital herpes by improving mood, reducing anxiety and loneliness which may serve as triggers for recurrent infections [22]. Lastly, patients can develop anger towards their current partner as questions regarding infidelity arise. Clinicians should remind patients that first time diagnosed outbreak does not necessarily imply new acquisition [1, 11, 23, 47, 48].

Patients need to be educated that HSV can be transmitted even when symptoms or genital lesions are absent, due to viral shedding. In addition, direct contact with mucous membranes or skin can lead to viral transmission, even in the absence of sexual intercourse. This fact is particularly important given that many young adults do not consider oral sex as sexual intercourse, and may therefore not recognize unprotected oral genital contact as a risk factor for HSV-1 transmission [10, 12, 47, 49]. All patients with genital HSV should be encouraged to inform their partners of their status, and if possible, partners should also be included in the counseling and education. In one study, the risk of HSV-2 transmission was approximately halved when infected individuals informed their partners of their HSV status [50].

Effective and consistent condom/barrier use is encouraged for all individuals or couples with genital HSV infection, and other sexually transmitted diseases. Condoms should be used during all sexual activity regardless of whether or not lesions are present and even in those who have never had symptoms (but have positive HSV-2 serology testing). Consistent condom use significantly decreases the risk of HSV-2 transmission, from men to women by 96% and from women to men by 65% [10, 43, 46]. Sexual activities should be discouraged entirely in the presence of lesions or prodromal symptoms, regardless of condom use. Chronic suppressive therapy should also be considered for sero-discordant couples, especially given that abstinence and consistent condom use may be challenging in the long term. Studies have shown that HSV transmission occurs frequently among partners who are monogamous and consider the relationship to be steady and therefore do not readily use condoms. Type-specific serologic testing of the asymptomatic partner should be

obtained prior to starting chronic suppressive therapy in order to confirm that the asymptomatic partner has not had previous acquisition of HSV. Long term treatment with valacyclovir (500 mg once daily) has been shown to lead to a significant reduction of viral shedding, oral acquisition of genital HSV-2 in uninfected partners, and is overall well tolerated [41–44].

Special Populations

HSV/AIDS

HSV-2 seroprevalence remains above average for high risk populations, such as sex workers, men who have sex with men, and HIV positive individuals. HSV-2 is a well-recognized risk factor for enhanced transmission of HIV; there is a two- to four-fold increased rate of HIV acquisition in those who have genital ulcers. The seroprevalence of HSV-2 infections in HIV-infected patients is high (50 to 90 percent), and most new diagnoses of HSV infection in HIV infected persons are non-primary due to prior acquisition of HSV-1 infection. Anogenital herpes was one of the first opportunistic infections described in persons with AIDS, and persistent herpetic ulceration is an AIDS-defining illness. Genital ulcers in HIV infected persons can be more frequent, severe, and of longer duration than in HIV-seronegative patient populations. HIV infected individuals with advanced immunosuppression (CD4 counts <100) may have persistent, extensive herpetic lesions that become deeply ulcerated and necrotic [50]. Due to the common atypical and severe manifestations, clinical diagnosis of HSV in HIV infected individuals may be unreliable. Diagnosis should be confirmed with PCR. Serologic HSV-2 testing remains controversial among HIV infected individuals, just as in HIV-negative individuals. Diagnostic utility is limited, as the majority of HIV-infected patients already have antibodies to HSV-1 and HSV-2 [28, 51].

HSV-2 helps to facilitate the acquisition of HIV via mucosal disruption, allowing entry of HIV, local influx of activated CD4+ cells which serve as a target cell for HIV attachment, and migration of activated lymphocytes to genital herpes resulting in increased local HIV replication on mucosal surfaces. These mechanisms are supported by studies demonstrating HIV virus isolated in HSV genital ulcerations and an increase in HIV viral load during HSV-2 reactivations in HIV+ positive individuals [43, 45, 52]. In addition, a study on the effects of anti-HSV medication in individuals with HSV-2 and HIV have shown strong and significant reduction in plasma and genital HIV-1 RNA levels associated with anti-viral treatment, suggesting that suppressive therapy of HSV-2 may reduce HIV-1 transmission via a reduction in genital and plasma HIV-1 RNA levels [53]. The degree of immunosuppression is an important factor in likelihood of HSV-2 reactivation; the rate of mucosal HSV- 2 shedding correlates directly with plasma HIV-1 RNA level and inversely with CD4+ cell counts. Shedding of HSV-2 is not only more frequent but also higher in quantity among HIV-infected persons with lower CD4+ cell counts [2, 3, 12, 14–15].

The principles of HSV treatment for HIV positive individuals are similar to that of individuals who are HIV negative. First-time episodes of HSV infection can be treated with the same antiviral agents – acyclovir, famiciclovir, and valacyclovir. However, the duration of treatment for an individual with HIV should extend until all lesions have completely healed in both initial and episodic outbreaks. Symptomatic outbreaks of genital herpes tend to respond more slowly too anti-HSV therapy in HIV-infected patients, especially patients with lower CD4+ cell counts, and higher doses of anti-herpes medications may be required for resolution of symptoms. Episodic therapy should last for a minimum of 5 days or until lesion resolution (which can be as long as 14 days), which can be significantly delayed when compared to HIV-uninfected persons (on average 3–5 days). Individuals with severe pain or significant systemic symptoms such as meningitis should be hospitalized for initiation of intravenous acyclovir treatment. If there is a lack of clinical response treatment, susceptibility testing should be considered to assess for possible acyclovir resistance. All acyclovir-resistant strains of HSV are also resistant to valacyclovir and famciclovir. Foscarnet and intravenous cidofovir are effective alternatives for treatment of acyclovir-resistant genital herpes; of note, however, both of these drugs have significant toxicities and require close laboratory monitoring. Consultation with an infectious diseases specialist is generally indicated for such patients. Imiquimod and cidofovir are also topical alternatives that can be considered in cases of acyclovir-resistant HSV [28].

Suppressive therapy has been shown to be less effective in HIV infected individuals who are not on antiretroviral therapy (ART). For individuals on ART, the use of suppressive therapy in the first three to 6 months may decrease the risk of HSV-2 genital ulcerative disease and shedding, particularly for those with a low CD4 count. In the US, current guidelines recommend the use of suppressive therapy to prevent genital ulcer disease in patients with a CD4 count <250 cells/mm [3] who are starting ART. If choosing an agent for suppressive treatment, physicians can use acyclovir, famciclovir or valacyclovir with BID or TID dosing. Once a day valacyclovir dosing should be avoided as it has been shown to be less effective. Duration of treatment should be discussed once the patient has regained immune function on ART as HSV recurrences should diminish with time. Physicians should reevaluate need for suppressive therapy annually once the patient's CD4 count is >200 cells/mm [3, 11, 43, 52].

Immune Reconstitution Inflammatory Syndrome (IRIS)

IRIS, also known as immune restoration disease, refers to a disease- or pathogen-specific inflammatory response in HIV-infected patients that may be triggered after initiation of ART. In individuals co-infected with HIV and HSV-2, there may be a transient increase in the incidence of genital ulcers within the first 3 months of ART. In addition, ART may be associated with an initial period of increased asymptomatic genital HSV shedding. The severity and frequency of HSV outbreaks

improve as the immune system is restored after HAART initiation, but patients with HSV-2 infection can present with severe manifestations even after their CD4+ cell count increases to normal levels. HSV-2 suppressive therapy can decrease the risk of HSV-2 genital ulcers and viral shedding after initiating antiretroviral therapy. Some studies have indicated that Acyclovir 400 mg twice daily may reduce the incidence of genital ulcers following initiation of ART and that viral shedding may fall back to baseline by 6 months of ART [2, 54, 55].

Pregnancy

When perinatal HSV transmission occurs, it is typically during labor and delivery as a result of direct contact with virus shed from infected sites (cervix, vagina, vulva, perianal area). Women with no past HSV history who develop lesions during pregnancy, or those with a history of genital ulcers but no prior laboratory confirmation, should have confirmatory PCR testing performed early in pregnancy. Type-specific HSV serology at the time of initial presentation is recommended for classifying maternal infection as primary, non-primary, or recurrent. Negative testing should be repeated about 1 month later in those with a high level of clinical suspicion to assess for possible seroconversion. Women who have a history of laboratory confirmed genital HSV prior to pregnancy do not need further testing. Management strategies for women who have genital herpes during pregnancy include suppressive antiviral therapy starting at 36 weeks to reduce the risk of recurrence at labor, and cesarean delivery for select women with active lesions or prodromal symptoms to reduce the risk of neonatal transmission. Women who present with their first lesions should be empirically started on antiviral therapy with acyclovir for 7–10 days. Recurrences are not always treated due to the desire to limit unnecessary fetal exposure to antivirals, but can be considered in those with severe and frequent symptoms. Acyclovir is categorized by the FDA as a category B medication, and Acyclovir Pregnancy held from 1984 to 1999 found there was no increase the number of birth defects identified among those exposures to acyclovir when compared with those expected in the general population [56, 57]. Other treatment alternatives such as ganciclovir and Foscarnet have more significant toxicities such as bone marrow suppression and decreased renal function and should be used with caution in pregnancy. Suppressive therapy at 36 weeks' gestation until delivery includes the administration of acyclovir three times daily (the substantial elevation in glomerular filtration rates seen in pregnant women can lead to more rapid drug elimination). Valacyclovir is not as well studied, but can be considered as an alternative if patient adherence is a concern because it is dosed twice daily. Transcervical procedures (e.g., cerclage, chorionic villus sampling) should be avoided in women with genital lesions to reduce the risk of infecting the placenta or membranes, but may be performed in asymptomatic patients. In addition, use of a fetal scalp electrode is also a potential risk factor for acquisition of neonatal HSV in women with asymptomatic viral shedding. Transabdominal procedures (e.g., amniocentesis, fetal blood sampling) are not

contraindicated in women with active genital disease. Caesarean delivery is recommended for those with active genital lesions (including those that have crusted) and prodromal syndromes [2, 5, 7, 28, 58].

Case Conclusion

One week later, the patient's vaginosis swab returned positive for Candida and BV, and her HSV PCR was positive for HSV-2. By the time of follow up, her symptoms had resolved. Education was provided regarding the natural history of genital herpes, risk of transmission, partner notification and additional treatment options. Additionally, HIV testing was performed, which turned out to be negative. She was given an additional prescription for valacyclovir to be taken in the event of possible recurrences.

Although this was her first outbreak, she could have been infected at any time since becoming sexually active, since initial infections can be subclinical. She was advised to refrain from sexual activity when she has active lesions, and consistently use condoms in order to reduce transmission.

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Chapter 17
Human Immunodeficiency Virus

Nikhil Ranadive, Sophia A. Hussen, and Rana Chakraborty

Case Study

An 18-year-old-male patient presents to the emergency department with fever, cough, and dyspnea that progressed over the course of 2 weeks. He describes feeling short of breath after attempting routine activities, such as climbing a flight of stairs. On further questioning, he reports receiving an HIV diagnosis at an urgent care clinic 2 years prior. Due to feeling "misunderstood" by his provider, he was lost to follow-up and has never received any treatment for his HIV infection. He denies any sexual activity since his diagnosis. Prior to his diagnosis, he engaged in receptive anal intercourse monogamously with his partner of 2 years, who was the first person he ever had sex with.

On physical examination, he has a temperature of 38.1 C. He is visibly tachypneic, and his pulmonary exam reveals rales and rhonchi on auscultation. Examination of his oropharynx is notable for white, adherent plaques on his palate and buccal mucosa.

A 4th-generation HIV antigen/antibody test is reported as positive. Subsequent laboratory testing results indicate a CD4+ T-cell count of 13 cells/μL and an HIV RNA (viral load) of over one million copies/μL. The plasma

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level of 1-3-beta-d-glucan – a component of the cell wall of the fungus *Pneumocystis jirovecii* – is elevated. Chest radiography demonstrates a diffuse, bilateral interstitial pulmonary infiltrate. The patient is diagnosed with AIDS and started on treatment for *Pneumocystis* pneumonia (PCP).

Questions

- What are the presenting symptoms of acute and advanced HIV infection?
- Which laboratory studies should be ordered prior to prescribing antiretroviral medications?
- What are the major opportunistic infections in patients with advanced AIDS?
- Why are young black men who have sex with men (YBMSM) at a disproportionately high risk for HIV infection?

Epidemiology

The human immunodeficiency virus (HIV) accounts for a substantial proportion of the global burden of disease among adolescents and young adults aged 10–24. As of 2015, HIV ranked third globally among the top causes of disability-adjusted life years (DALYs) lost in children and teens aged 10–14 years, tenth among adolescents aged 15–19, and seventh among youth aged 20–24 [1]. The prevalence of HIV infection among youth in the United States (US) is also high. As of 2013, there were 6537 HIV-positive adolescents (aged 13–19) and 32,980 HIV-positive young adults (aged 20–24) living in the United States [2]. Adolescents and young adults in the United States represent a uniquely challenging group to provide care for, compared with older HIV-infected adults [3]. Data from 2012 showed that only 66% of HIV-infected youth aged 13–24 were engaged in care within a month of diagnosis, ranking lowest out of any age group in this domain [4]. Adolescents and young adults are also least likely to maintain an undetectable HIV viral load (which is the ultimate goal of therapy with HIV medications), with data from 2012 indicating that only 38.0% of HIV-infected youth had reached this goal [4].

Racial disparities in HIV prevalence and incidence also exist among adolescents and young adults. For example, in 2014, the incidence of HIV was 20 times greater in black adolescents as compared to white adolescents [2]. This discrepancy is even more pronounced with the rate of AIDS diagnoses, which, in the same year, was 41 times greater in the former group [2].

The relative importance of different modes of HIV transmission varies by age group, gender, and sexual behaviors. Among 3766 HIV-positive young adolescent males (aged 13–19) in 2013, 49% were infected through male-male sexual contact, 43% through vertical [perinatal] transmission, and 2% through heterosexual contact. In contrast, among the 26,008 HIV-positive young adult males (aged 20–24), 85% were infected by male-male sexual contact, 7% vertically, and 3% by

heterosexual intercourse. A smaller number of females in both age categories were infected: 2770 15–19-year-olds and 6972 20–24-year-olds, respectively. While the majority of female 15–19-year-olds were infected by vertical transmission from their mothers at birth (69%), 63% of female 20–24-year-old young adults were infected by heterosexual contact [2].

Microbiology and Pathophysiology

The HIV Life Cycle

HIV is a retrovirus that impairs the immune system by primarily infecting CD4+ helper T-cells and "hijacking" intracellular DNA [5]. The HIV life cycle can be divided into seven discrete stages (Fig. 17.1). *(1)* The viral glycoprotein 120 (gp120) *binds* to the CD4 receptor on activated CD4+ T lymphocytes or other cells that express this ligand, such as resting CD4+ T cells, monocytes, macrophages, and dendritic cells. This induces a conformational change in the virus such that it can bind to a second co-receptor: either the CC-chemokine receptor 5 CCR5, most often, or to the CXC-chemokine receptor 4 (CXCR4) [5–7]. *(2)* Following co-receptor binding, viral gp41 protein becomes exposed on the surface of the virus, which facilitates *fusion*, whereby the virion and target cell are brought closer together. Fusion allows a "pre-integration complex," comprised of viral proteins, enzymes, and RNA, to be released into the cytoplasm [5]. *(3)* The third step is *reverse transcription: i*n the cytoplasm of the T-helper cell, HIV reverse transcriptase converts single-stranded HIV RNA into double-stranded DNA. *(4)* The newly synthesized DNA then *integrates* into the host genome using the viral enzyme *integrase* [5, 7]. *(5) Replication* of viral DNA occurs when host enzymes transcribe viral mRNA and translate viral proenzyme. *(6)* Following glycosylation, phosphorylation, and cleavage of the proenzyme, the newly synthesized HIV proteins and RNA migrate to the T-cell surface in a step called *assembly*. *(7)* The final step, *budding*, involves the release of HIV from host cells, typically at lipid rafts along the cell membrane [5, 7].

Acute HIV Infection

HIV transmission occurs at mucosal membranes through infection by a founder virus that replicates via the pathways described above [6, 8]. Acute HIV infection commonly presents with nonspecific clinical manifestations such as fever, headache, and malaise. Physical examination may reveal tachycardia and lymphadenopathy. Patients may also present with diffuse maculopapular skin rash, pharyngitis, myalgias, night sweats, arthralgias, and/or diarrhea [9–11].

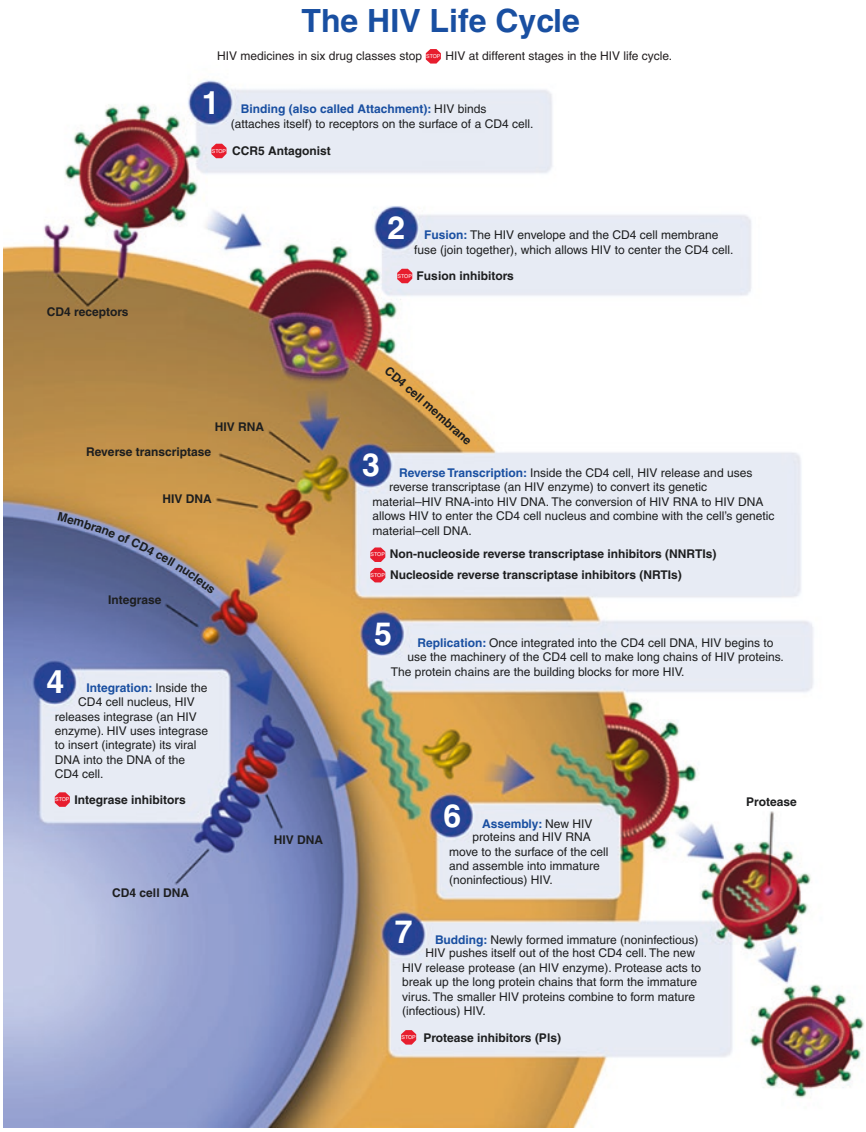

Fig. 17.1 The HIV life cycle and associated antiretroviral medication targets. (Reprinted with permission from the National Institutes of Health (NIH [120]))

The symptoms of acute HIV infection correlate closely with viral dynamics. Acute infection is characterized by an initial surge in plasma HIV RNA, and clinical manifestations are most salient at the peak of viremia [10, 12]. However, these symptoms are transient and subside once the host's innate and adaptive immune responses become activated, which results in a drop in viral load to a newly defined

"set point," typically established within 18–42 days from when viral RNA is first detectable [10]. This set point is an important prognostic indicator, with higher set points being predictive of rapid progression to AIDS [12–15].

Immune Response and Dysfunction

While CD4+ helper T-cell and CD8+ T-lymphocyte counts maintain homeostasis during initial infection, peak viremia during acute infection corresponds with an immunophenotypical shift associated with a precipitous decrease in CD4+ T cells [10, 16–18]. The marked reduction in CD4+ cells and subsequent impairment of the immune system is a hallmark of HIV infection [6]. While there is some reconstitution and recovery of CD4+ cells following this initial decrease during acute infection, in the absence of treatment with antiretroviral therapy (ART), this number continues to decrease over a variable time period [6]. Additionally, while CD8+ T cells may be able to initially reduce viremia, they are incapable of clearing the infection due to viral evasion of host defenses (including development of escape mutants as well as intracellular persistence within viral reservoirs) [19, 20]. These reservoirs develop following latent infection of resting memory T cells including those within lymphoid tissue, the central nervous system (CNS), and the gastrointestinal (GI) tract [21–24], allowing HIV to persist in a dormant state even once the patient has been started on effective ART.

Other correlates of adaptive immunity include the evolution of humoral immune responses; however, the virus quickly evolves to evade the humoral immune system through escape mutants [25]. The production of IgM and IgG antibodies to HIV serve as useful serological markers for the detection of HIV infection.

Chronic Inflammation and Progression to AIDS

While the gradual depletion of CD4+ cells is more commonly asymptomatic, HIV infection results in a state of chronic inflammation and immune activation, which in turn is associated with depletion of CD4+ cells in the GI tract – an insult which only minimally recovers with effective ART [6, 26]. This GI tract depletion includes loss of T-helper 17 as well as mucosal-associated invariant T cells, both of which play important roles fighting bacterial enteropathogens [27, 28]. The resulting increased gut permeability to bacterial products (e.g., lipopolysaccharides) exacerbates immune activation [29] and is associated with a number of adverse health outcomes, including cardiovascular disease and malignancy [30–34].

The vast majority of untreated patients will eventually progress to acquired immunodeficiency syndrome (AIDS), also referred to as Stage 3 HIV infection by the Centers for Disease Control and Prevention (CDC). AIDS is defined by a CD4 count below 200 cells/μL or a development of an AIDS-defining illness [35, 36].

Table 17.1 Stage 3: defining opportunistic illness in HIV infection, as defined by the CDC

Candidiasis of bronchi, trachea, or lungs
Candidiasis of esophagus
Cervical cancer, invasive
Coccidioidomycosis, disseminated or extrapulmonary
Cryptococcus, extrapulmonary
Cryptosporidiosis, chronic intestinal (>1 month's duration)
Cytomegalovirus disease (other than liver, spleen, or nodes)
Cytomegalovirus retinitis (with loss of vision)
Encephalopathy attributed to HIV
Herpes simplex: chronic ulcers (>1 month's duration) or bronchitis, pneumonitis, or esophagitis
Histoplasmosis, disseminated or extrapulmonary
Isosporiasis, chronic intestinal (>1 month's duration)
Kaposi sarcoma
Lymphoma, Burkitt
Lymphoma, immunoblastic
Lymphoma, primary, of brain
Mycobacterium avium complex or *Mycobacterium kansasii*, disseminated or extrapulmonary
Mycobacterium tuberculosis of any site
Mycobacterium, other species, disseminated or extrapulmonary
Pneumocystis jirovecii [PCP] pneumonia
Pneumonia, recurrent
Progressive multifocal leukoencephalopathy
Salmonella septicemia, recurrent
Toxoplasmosis of brain
Wasting syndrome attributed to HIV

The immunocompromised state resulting from CD4 depletion below 200 cells/μL predisposes HIV-infected individuals to a host of characteristic opportunistic infections and malignancies [36]. A detailed list of these AIDS-defining illnesses is listed in Table 17.1.

Diagnostic Testing

HIV diagnostic testing has become significantly more accurate and timely over the past two decades. There are now four generations of immunoassays used to detect immune response to HIV, in addition to nucleic acid testing (NAT) that can directly detect viral genetic material [37–39]. Each new generation of tests detects HIV

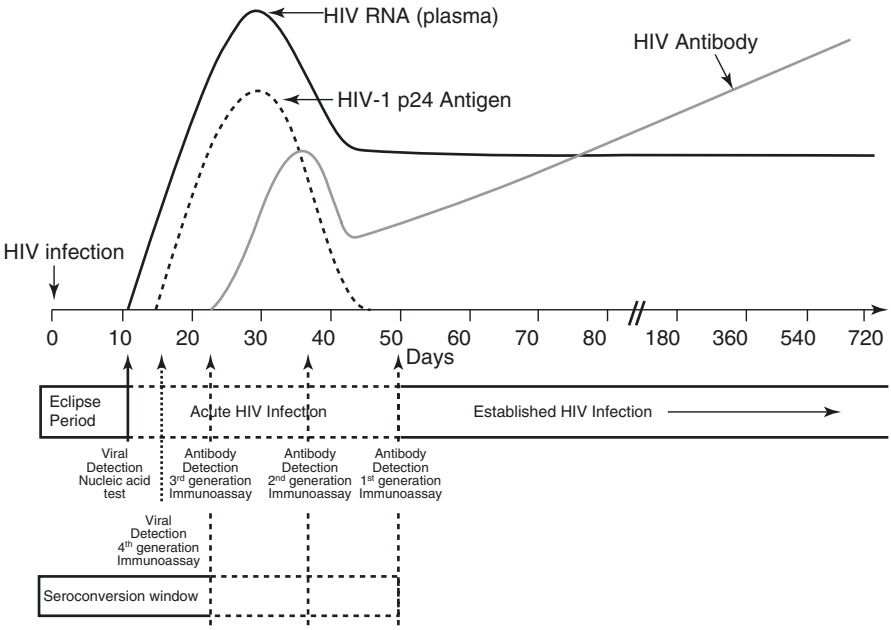

Fig. 17.2 Sequence of appearance of laboratory markers for HIV-1 infection. (Reprinted with permission from the Centers for Disease Control and Prevention (Branson et al. [39]))

earlier in infection compared to the older generation(s). This sequential reactivity of HIV assays has allowed for the designation of four distinct laboratory stages: *(1)* the eclipse period, *(2)* acute HIV infection, *(3)* the seroconversion window, and *(4)* established HIV infection (Fig. 17.2) [40–44]. Early detection of HIV is critical for both individual and public health outcomes. Early diagnosis can reduce secondary HIV transmission from acutely infected individuals, who have high levels of viremia (making them more likely to transmit the virus) and may not know how to reduce their risk behaviors [45, 46]. Earlier initiation of ART also results in significantly improved clinical outcomes in infected subjects [47].

In the *eclipse period,* there are no assays that can reliably detect HIV infection. *Acute HIV infection,* characterized by a spike in viral RNA, is detectable by NAT within 10 days of infection [38, 48–51]. The *seroconversion window* refers to an interval between initial HIV infection and when an antibody or antibody/antigen combination immunoassay can reliably detect infection. The timing of this window varies slightly by the type of assay [41]. For instance, fourth-generation antigen/antibody immunoassays can detect HIV-1 p24 antigen 4–10 days after HIV-1 RNA becomes detectable by NAT [43]. Third (as well as fourth)-generation immunoassays detect IgM antibodies 10–13 days after the appearance of viral RNA [39, 41–43, 52]. Older immunoassays detect IgG during the interval of *established infection*, 18–38 days following the appearance of viral RNA [39, 41–43, 53]. New guidelines by the Centers for Disease Control and Prevention (CDC) and the Association of Public Health Laboratories (APHL) incorporate the use of newer generation

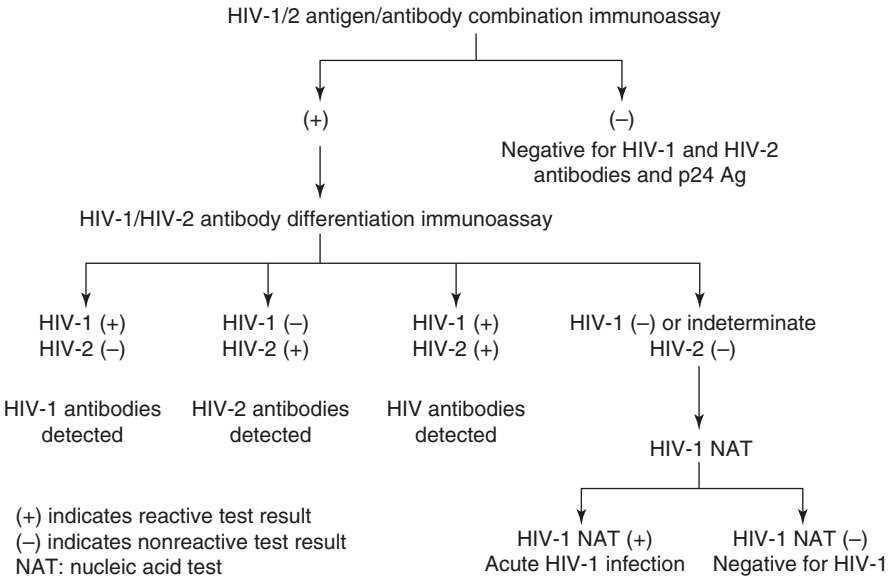

Fig. 17.3 Recommended laboratory HIV testing algorithm for serum or plasma specimens. (Reprinted with permission from the Centers for Disease Control and Prevention (Branson et al. [39]))

antigen/antibody combination immunoassays in combination with NAT [39]. This algorithm (Fig. 17.3) has been shown to be more effective at detecting acute and newly established infections compared to older algorithms using Western blot testing [39]. Individuals with suspected HIV infection should be tested with the latest generation FDA-approved two-step antigen/antibody immunoassays. A positive test could be indicative of established HIV-1 or HIV-2 infection or an acute HIV-1 infection [39]. The second step distinguishes between HIV-1 and HIV-2 through further testing with antibody immunoassays specific to the two different strains [39]. (Note: HIV-2 is a strain of HIV that is highly unusual in the United States – there are some subtle differences in natural history and treatment recommendations that are beyond the scope of this chapter, which is focused on HIV-1 infection). If this step yields indeterminate or negative results, nucleic acid testing can differentiate between acute and established HIV-1 infection or, if negative, indicate false positivity of the initial antigen/antibody immunoassay used at the point of care [39].

Treatment

Antiretroviral therapy (ART) has markedly improved in efficacy and tolerability since the implementation of combination therapy in 1996, resulting in substantial declines in HIV and antiretroviral (ARV)-related morbidity and mortality [47, 54].

ART essentially transformed HIV into a chronic condition, so that patients who are able to maintain medication adherence have a life expectancy comparable to that of the general population [55, 56]. Here we discuss treatment guidelines from the Department of Health and Human Services that are informed by expert opinion and scientific evidence [57]. While we summarize some principles of managing HIV-infected patients, it should be noted that HIV management is a complex and nuanced process. Studies have shown that HIV-infected subjects have better clinical outcomes when they receive care from clinicians with expertise and training in HIV medicine (i.e., those who are actively treating at least 20 patients with HIV). Whenever possible, patients should be referred to receive care from providers experienced in HIV/AIDS care [58–62].

Ideally, all HIV-infected individuals should receive ART as soon as baseline laboratory tests have been obtained and an assessment has been made regarding the patient's barriers and facilitators to medication adherence. Baseline evaluation should include a complete medical history, physical examination, blood draw for laboratory investigations, and counseling about the pathophysiology, clinical course, and treatments of HIV [57]. The two most important lab tests are to assess two important markers: *CD4+ T-lymphocyte count* and *plasma levels of HIV RNA or HIV viral load* [15, 57, 63]. The CD4+ T-cell count gives an estimate of the level of immunocompromised (or lack thereof). HIV-uninfected individuals typically have CD4+ values ranging between approximately 450 and 1000 – in patients with HIV, a CD4+ count under 200 cells/μL indicates severe immunocompromised and a need to prescribe prophylaxis against opportunistic infections [64]. The viral load, in contrast, is a marker of how well a patient is responding to ART. The goal of treatment is to achieve an undetectable level of viremia (although it should be noted that the limit of detection varies by assay and can range from <20 to 75 copies of virus/μL) [57]. A viral load of greater than 200 copies/μL is suggestive of virologic failure [65]. This could be due to the development of viral resistance to the ART regimen in use, nonadherence to medications, or both. Both CD4 counts and viral load testing are monitored during clinic appointments, with viral load being the most important marker of continued adherence and medication efficacy [57].

Patients should also undergo baseline drug resistance testing and genetic screening for the HLA B∗5701 allele. Drug resistance testing helps guide which ARVs are active against the patient's virus and has been shown to improve virological outcomes when incorporated into HIV-management decision-making [57, 66]. In most patients, initiation of ART should be delayed until receiving results of the resistance testing [57, 67]. However, in HIV-infected pregnant women and patients presenting with acute infection, it is recommended to initiate therapy immediately and adjust the regimen later, as necessary [57]. Clinicians can order either genotypic or phenotypic assays to assess for resistance, both of which have been shown to be effective in guiding selection of ARVs [68]. Genotypic assays involve HIV-1 gene sequencing, which allows for detection of mutations that confer resistance [57, 67]. Phenotypic assays, conversely, are culture-based and measure the ability of HIV to grow at different concentrations of ARVs [57, 67]. It should be noted that the absence of detected resistance on the baseline evaluation does not mean that no viral

resistance is present. The wild-type (non-mutated) version of the HIV virus is more genetically fit and tends to overgrow other strains in the absence of selective pressure induced by medications. Therefore, those patients whose viral loads are not suppressed within the expected time frame (1–2 months) should have repeat resistance testing done while on ART. Finally, patients should be screened for HLA B∗5701 allele, prior to initiating ART that contains the ARV abacavir, which can cause a life-threatening hypersensitivity reaction in individuals who are HLAB∗5701 positive [69–71].

The main goals of therapy are to suppress viremia beneath the level of detection, restore immunologic function, reduce long-term HIV- and ARV-associated morbidity, and prevent onward secondary HIV transmission [57]. This requires selection of an ARV regimen that the virus is susceptible to and that the patient will be able to adhere to. To guide this process, important considerations include drug interactions, side effects, susceptibility and resistance, and "pill burden," which vary widely across different ARV classes [57]. The current standard is to prescribe ART comprised of three different ARVs from two different classes. ARV classes include nucleos(t)ide reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), integrase strand transfer inhibitors (INSTIs), and fusion inhibitors [57]. A schematic of where these medications intervene in the HIV life cycle is depicted in Fig. 17.1. The most commonly prescribed regimens involve two NRTIs with a medication from a second class [57]. Figure 17.4 lists all currently available medications (at the time of this writing), their major side effects, and special considerations unique to these ARVs. Of note, ARV regimens and recommendations are frequently changing; we recommend consulting the Department of Health and Human Services guidelines (https://aidsinfo.nih.gov/guidelines) for the most up-to-date recommendations.

Early initiation of ART is strongly recommended in pregnant women, in order to reduce the risk of vertical transmission. Most ARVs have not been associated with teratogenic effects beyond those observed in the general population [72], although there are concerns related to a higher rate of preterm delivery and low birth weight infants born to HIV-infected mothers [72, 73]. Current guidelines recommend standard combination ART (i.e., 2 NRTIs with a ritonavir-boosted PI, INSTI, or NNRTI). Previously, efavirenz was not recommended during pregnancy due to concern for increased rates of central nervous system anomalies in the fetus – this warning has largely been discredited, and use of efavirenz is no longer restricted based on sex or pregnancy [74]. Recently, researchers in Botswana noted a higher rate of neural tube defects among children born to women who were taking dolutegravir at the time of conception – this was a small observation of only four infants but represented a significant deviation from the expected rate [75]. Further study is warranted to determine the implications of this observation, and there has been no change in official recommendations at the time of this writing; however, clinicians may want to consider other options besides dolutegravir for young women who are planning on becoming pregnant (or who are of childbearing age but not being prescribed effective contraception). See Fig. 17.4 for ART recommendations during pregnancy.

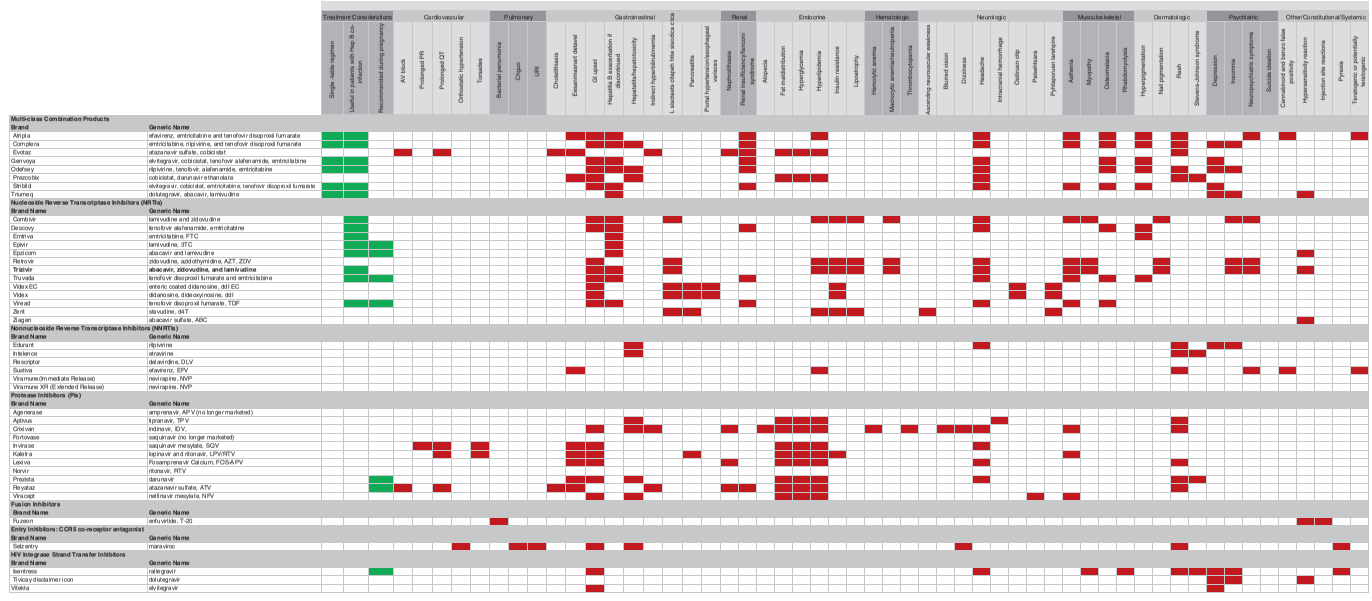

Fig. 17.4 Classes of antiretroviral medications for the treatment of HIV, including beneficial treatment considerations (green boxes) and major side effects (red boxes)

Prevention

A number of evidence-based behavioral and biomedical interventions exist to prevent the transmission and acquisition of HIV, including educational programs, male and female condoms, male circumcision, pre- and postexposure prophylaxis, and treatment as prevention. Here we discuss the efficacy and effectiveness of some of these interventions in adolescents and young adults, as well as their limitations.

Sexual Education

Comprehensive sexual education is an important component of reducing sexual risk behaviors in adolescents. While there is conflicting evidence, there is general consensus that "risk reduction" programs [i.e., programs that teach safe sexual practices] are more effective at decreasing risky behaviors compared to "risk avoidance" programs [i.e., programs that advocate for delaying initiation of sexual activity] [76].

Risk reduction programs typically target knowledge, perceptions of risk, values about sexuality, self-efficacy to refuse sexual activity, communication with parents and other adults, and self-efficacy to obtain and/or use condoms. They have been shown to decrease the average number of sexual partners, increase the use of condoms, and reduce the incidence of HIV transmission among adolescents [76, 77]. While some studies have shown that abstinence education may result in safer sexual practices, the evidence base is lacking [78].

In practice, the implementation of sexual education curricula varies across the United States. The majority of US schools do not teach all of the content recommended by the CDC [79]. High-risk populations may be particularly disadvantaged by this. For instance, young MSM engaging in risky sexual behaviors have reported that the education they received in school catered exclusively to heterosexual partnerships. This lack of comprehensive sexual education may undermine efforts to reduce in the incidence of HIV infection [80]. Medical providers can therefore play a critically important role in sexual education that is not being provided in schools. Studies have shown that even single-session risk reduction interventions are significantly associated with decreased unprotected sex acts and a decreased risk for STI infection [81].

Male and Female Condoms

The efficacy of male condoms vary depending on the type of sexual activity and are contingent on their consistent use. Among heterosexuals engaging in penetrative vaginal intercourse, consistent use of condoms (defined as use of condoms every

time sex is initiated) reduces the risk of HIV transmission by as much as 80% [82]. While the evidence is lacking, condoms appear to be less effective at preventing HIV transmission during anal intercourse. Condom breakage and slippage are reported frequently by young MSM and associated with STI transmission events [83]. A common practice, especially among black MSM, is to use oil-based and other hyperosmolar lubricants in conjunction with condoms. These have been linked to decreased strength of condoms as well as epithelial damage in the rectum, which in turn may increase the risk of HIV transmission and acquisition [83–85]. Lastly female condoms have been shown to be just as efficacious and to confer just as much protection from STIs as male condoms among heterosexuals during penetrative vaginal sex [86].

Biomedical and Surgical Interventions

A number of biomedical and surgical interventions have been shown to be effective at reducing the risk of HIV transmission and acquisition. These include male circumcision, which has been shown to reduce the risk of HIV acquisition by 38–66% over a 24-month period among males specifically during heterosexual sex [87]. Circumcision may also be protective among MSM engaging in insertive anal sex; however, data are limited, and the benefits are especially unclear for receptive partners [88].

Preexposure prophylaxis (PrEP) with tenofovir-emtricitabine (TDF-FTC) has been shown to reduce the risk of HIV acquisition in MSM, serodiscordant couples, and among other high-risk populations [89]. At the time of this writing, TDF-FTC (which consists of two active drugs against HIV, *not* a complete ART regimen) is the only approved regimen for PrEP – it requires patients to take one pill, once daily as a method for preventing HIV acquisition. CDC guidelines are available and recommend consideration of PrEP for HIV-negative MSM (including behaviorally bisexual men) who report *any* unprotected anal intercourse in the past 6 months (outside of a monogamous relationship with a confirmed HIV-negative partner) or any bacterial STI in the last 6 months. Uptake of PrEP has been much lower for heterosexual men and women, but it should be noted that guidelines also recommend considering PrEP for heterosexual individuals who are sexually active (within the past 6 months) and are diagnosed with bacterial STI within the last 6 months OR report infrequent condom use with partners who are at risk for HIV or known to be HIV-positive [90]. As of May 2018, the US Food and Drug Administration has expanded approval to include high-risk adolescents including those under 18 years of age (provided they weigh at least 35 kg) [91]. Of note, however, the study that led to this approval did demonstrate low rates of adherence to PrEP, suggesting that intensive adherence counseling and monitoring are warranted when prescribing PrEP in this youth population [92]. Prescribing of PrEP requires close follow-up with regular STI and HIV testing, as well as monitoring of renal function (which can be adversely impacted by tenofovir). For more guidance about PrEP, clinicians

can refer to the CDC guidelines (available online: https://www.cdc.gov/hiv/pdf/risk/prep/cdc-hiv-prep-guidelines-2017.pdf) and/or call the National Clinicians Consultation Center PrEPline at 855-448-7737.

Postexposure prophylaxis (PEP) can also be considered for adolescents and young adults after a high-risk exposure. Non-occupational PEP, or nPEP, encompasses sexual exposures that would be more likely than occupational exposures (i.e., needlestick injuries) in the adolescent population. Following exposure to an individual known or thought to be HIV-infected, persons being considered for nPEP must be tested for HIV – however; dependent on the level of concern for transmission and rapidity of available testing modalities, one does not need to wait for results to start a patient on nPEP [93]. In fact, PEP should be initiated within 72 hours of exposure and discontinued if the potential source of infection is determined to be HIV-negative [93]. nPEP is *not* recommended when the exposure occurred greater than 72 hours prior to presentation. The CDC currently recommends tenofovir-emtricitabine once daily *plus* raltegravir twice daily OR dolutegravir once daily or alternatively tenofovir-emtricitabine once daily with ritonavir and darunavir once daily – in contrast to PrEP, these are complete ART regimens that are also recommended for HIV-positive individuals [93]. *Receipt of one or more courses of nPEP within a year should lead a clinician to consider prescribing the patient daily PrEP as opposed to multiple 28-day courses of nPEP.* Additional information is available in the CDC PEP guidelines (available online: https://www.cdc.gov/hiv/pdf/programresources/cdc-hiv-npep-guidelines.pdf), and consultative assistance is also available from the National Clinicians Consultation Center PEPline at 888-448-4911.

Finally, the single most efficacious form of biomedical HIV prevention is what is referred to as *treatment as prevention* (TasP). TasP refers to the now well-supported idea that effective ARV treatment associated with viral suppression prevents further viral transmission. A number of large studies have shown that early (as opposed to delayed) initiation of ART with subsequent viral suppression is highly effective at preventing secondary HIV transmission among serodiscordant partners, including heterosexuals as well as MSM [94–96]. As an extension of this idea, the risk of perinatal transmission among HIV-infected women giving birth has also been shown to be low – 0.09–0.4% in virologically suppressed mothers who were effectively treated with ART for greater than 4 weeks [97, 98]. The risk of HIV transmission is particularly low for virologically suppressed mothers who initiate care prior to conception [99]. Based on this strong base of scientific evidence, the CDC has endorsed an educational campaign entitled “U=U” or “Undetectable = Untransmittable” to convey to the public the low risk of HIV transmission from individuals who are regularly engaged in care and adherent to their medications. In summary, these data provide support for an encouraging message that clinicians can pass on to their patients with respect to future sexual encounters: although HIV disclosure is still advised and condom use is still recommended to prevent other STIs, patients who maintain an undetectable viral load can feel confident that they are not transmitting HIV to their sexual partners.

Special Considerations

HIV-infected individuals are subject to a number of contextual and socioeconomic factors that warrant consideration by clinicians. Low socioeconomic standing (SES) is significantly associated with higher HIV diagnosis rates in low-income young MSM and across different racial groups [100, 101]. HIV/AIDS also discriminates spatially, such that AIDS prevalence is significantly and independently associated with neighborhood disadvantage, even after controlling for race [102]. HIV-infected persons also have lower survival rates if they live in low-income areas [103]. Other important contextual factors include housing stability and food insecurity. Unstable housing and homelessness among HIV-infected individuals including youth have been linked to riskier sex behaviors such as an increased number of partners and decreased condom use [104–107]. Similarly, food insecurity among HIV-positive individuals has been linked to a number of risk behaviors, including transactional sex and ARV and medical appointment non-adherence [108–111]. It is critical for clinicians to adapt treatment plans to meet unique individual needs and to work with patients to address contextual barriers that adversely affect treatment outcomes.

It is also critical for clinicians to understand the role of stigma and how this can affect medical care. Stigma in HIV-infected individuals is a cause for delayed seeking of medical care and ART and medical appointment nonadherence [112–114]. Patients have disengaged from care when they felt that their providers were not listening to their concerns or appeared to dislike caring for them [115, 116]. Given that medical adherence is the cornerstone of a successful treatment regimen, it is crucial for clinicians to develop rapport with their patients in a nonjudgmental way.

This brings us to our final point: the relationship between race, sexual orientation, and HIV. Young black MSM have a disproportionately high incidence and prevalence rate of HIV as compared to other demographic and age groups. However, they have also been shown to have *less risky* behaviors, including a *lower* number of sex partners and *lower* instances of unprotected sex compared to young MSM of other races [117]. It is now well established that individual-level factors do not explain the black-white disparity in HIV rates among young MSM. While more investigation is warranted, it is thought that this disparity can be explained at least in part by contextual factors (i.e., the social determinants of health) and engagement of black MSM within a smaller sexual network with a higher background HIV prevalence rate [118, 119].

Case Conclusion

In addition to treatment for *Pneumocystis* pneumonia, the patient was referred to an outpatient physician specializing in HIV care. His complete blood count, CD4+ T-cell count, HIV viral load, HIV genotype resistance testing, and screening test for HLA0B∗5701 positivity were obtained. Titers were ordered for hepatitis B exposure.

He also received a full STI screen including testing for gonorrhea, syphilis, chlamydia, trichomoniasis, and hepatitis A, B, and C.

The majority of the visit was spent discussing the patient's life circumstances, including an assessment of the patient's social support, ability to adhere to medications, sexual history, and mental health. The patient reported that he previously disengaged from care after his provider made him feel badly about his sexual behaviors. The patient also admits feeling like he is "not clean" after receiving his diagnosis and explains that as the reason for ceasing sexual activity since his initial diagnosis. He reports that while he is depressed and unemployed, he is currently living with his older sister, who is able to financially support him. The provider explains to the patient that the risk of HIV transmission is negligible in virologically suppressed persons, discusses the complications of HIV and the side effects of treatment, and refers him to a psychiatrist or psychologist and case manager for additional support. The patient is negative for HLA0B∗5701, and titers reveal that he was vaccinated and is now immune to hepatitis B. On a follow-up visit, the HIV provider prescribes a fixed-dose combination pill of ART to be taken once daily and asks him to follow up in 2–4 weeks in order to assess adherence, inquire about any side effects, and re-measure the HIV viral load, looking for a 1–2 log reduction in this value.

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Chapter 18
Human Papillomavirus (HPV)

Amelia B. Thompson and Lisa C. Flowers

Case Presentation

A 23-year-old male presented to his primary care clinic with complaints of intermittent bloody stools and weight loss. He had a history of hemorrhoids and attributed his bloody stools to their recurrence. He did not receive the HPV vaccine. He reported having insertive and receptive sexual intercourse with male partners only, and estimated that he had 20 lifetime sexual partners since his sexual debut at age 15 years. Physical examination identified hemorrhoids, and anal cytology revealed atypical squamous cells of undetermined significance (ASCUS). He underwent examination under anesthesia with biopsies by the general surgery team. His biopsies showed *condyloma acuminata* (genital warts) and several foci of low- and high-grade dysplasia (LSIL and HSIL respectively) and carcinoma in situ. The pathology was highly suggestive of invasive carcinoma and so his primary physician referred him to an oncologist, who planned for the patient to undergo surgical excision of the lesions followed by chemotherapy with 5-fluorouracil and mitomycin C with concurrent radiation therapy.

Questions:

1. What is the significance of an abnormal cytological result?
2. How does one treat genital warts?
3. What are the current recommendations for preventing HPV-associated diseases?

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Epidemiology

Genital HPV is the most common STI in the United States, and adolescents and young adults (ages 15–29) account for 49% of all new cases [1]. HPV is transmitted via skin-to-skin contact, vaginal, anal or oral sexual intercourse, manual sexual activity, autoinoculation, in utero and during vaginal delivery [2, 3]. Transmission via fomites, particularly sex toys, is possible even after routine cleaning procedures due to the resilient nature of the virus [4, 5]. Genital HPV acquisition is associated with young age, early age at sexual debut, unprotected sexual intercourse, number of lifetime sexual partners and a history of other STIs [3, 6]. The probability that a sexually active person will acquire HPV infection at least once in her/his lifetime ranges from 54% to 98%, but these are generally asymptomatic, self-limited infections [7–9]. Up to 90% of all new HPV infections resolve within 2 years after infection, but 7% persist after 5 years [10]. Persistent HPV infection can cause cervical, vulvar and vaginal cancers in women, penile cancers in men and anorectal and oropharyngeal cancers in women and men [8, 11, 12].

The first HPV vaccine, quadrivalent (4v) HPV (Gardasil®, Merck and Co, Inc.), was licensed for use in the United States in 2006. Since then, vaccine-type prevalence of HPV infection (HPV-6, -11, -16, and -18) has declined significantly in adolescent and young adult females; from 11.5% to 4.3% in the 14 to 19 years age group and from 18.5% to 12.1% in the 20 to 24 years age group [13]. The full impact of HPV vaccination on cytological abnormalities is currently unclear. However, the risk of cervical cytology abnormality is lower among vaccinated females compared with those who are unvaccinated in the United States, with increased protective effect noted in women who completed the vaccine series between 11 and 14 years of age [14].

Microbiology

HPV is a small, non-enveloped, double-stranded DNA virus that belongs to the family *Papillomaviridae* [15]. More than 150 HPV serotypes exist [16], and the World Health Organization has recognized 13 of these as carcinogens [17]. An additional 15 types are 'possibly' cancer-causing due to limited evidence in humans. HPV types 16 and 18 are thought to be the most prevalent "high-risk" types, whereas 6 and 11 are considered "low-risk" or non-oncogenic types [3]. The HPV genome exists as circular extrachromosomal genetic material (episome), that replicates independently and is comprised of three regions: an upstream regulatory region (URR), the early (E) region and the late (L) region [18]. The E region has six open reading frames (ORFs): E1–2 and E4–5, which encode the proteins required for viral replication, as well as E6–7, which bind the p53 tumor suppressor and the retinoblastoma tumor suppressor (pRb) proteins respectively. The L region contains two ORFs that encode the structural proteins of the capsid, L1 and L2, as well as a non-coding region that is required for the HPV life cycle [15, 18–20] (Table 18.1).

Table 18.1 Roles of the HPV viral proteins

	Protein	Mechanism
Early	E1	ATP-dependent DNA helicase; involved in viral replication
	E2	Regulates cell cycle and apoptosis, viral replication, represses E6 and E7
	E4	Regulates cell cycle arrest, viral assembly and release
	E5	Oncoprotein; interacts with epidermal growth factor receptor, controls cell growth and differentiation
	E6	Oncoprotein; binds and degrades p53, inhibits apoptosis and differentiation
	E7	Oncoprotein; binds and degrades pRb, involved in cell cycle control
Late	L1	Major capsid protein
	L2	Minor capsid protein, recruits L1, viral assembly

Pathophysiology

Viral Replication

HPV infects squamous epithelial cells through breaks in the skin or minor abrasions [15, 18]. The virus interacts with proteoglycans and integrins on the surface of keratinocytes in the basal epidermal layer. Viral endocytosis and capsid disassembly follow [21, 22]. The viral genome initially remains in its episomal form and expression is controlled without associated inflammation. After the virus replicates, the capsid proteins are expressed and assembled. The E4 protein then facilitates release of the mature virion [15, 19, 23]. The vast majority of HPV infections resolve completely without overt clinical disease. An additional proportion of infected persons develop benign lesions which eventually regress due to the cell-mediated immune response [23]. However, some HPV episomes may persist in basal epithelial cells with the potential to reactivate in the future [24].

Oncogenesis

Persistent infection develops when the cell-mediated immune response fails to clear the virus. As the infection progresses, the viral DNA integrates into the host genome with loss of the E1 and E2 genes. The loss of E2 leads to increased E6 and E7 oncoprotein expression [15, 19, 25]. In normal human physiology, the tumor suppressor p53 arrests the cell cycle in the Gap 1 (G1) phase to allow for repair of DNA damage. If the damage is irreparable, it induces cellular apoptosis [15]. When the E6 protein from high-risk HPV types is upregulated, it facilitates the degradation of p53, which results in higher mutation rates and decreased host cell apoptosis [26–30]. Similarly, HPV E7 proteins mediate dysplasia and oncogenesis by enhancing phosphorylation and destruction of the retinoblastoma protein (pRb). As a result, cell cycle entry and cellular proliferation are stimulated in an unregulated fashion [19, 23].

Clinical Manifestations

HPV causes a variety of conditions ranging in severity from genital warts to squamous cell carcinoma. Types 6 and 11 primarily cause genital warts. They may be discrete lesions or appear in clusters, be flesh-colored or hyper-pigmented, flat, papular or pedunculated in shape, and smooth, verrucous or keratotic in texture [31, 32]. Warts may occur on any part of the anogenital region including, but not limited to the labia, clitoris, perineum, perianal region and anal canal (Fig. 18.1). Bowenoid papulosis is a rare clinical manifestation of HPV infection, which consists of groups of well-demarcated hyperpigmented papules. Despite its benign clinical appearance, it is most commonly due to infection with the high-risk type HPV-16, and sometimes histology reveals features of cellular dysplasia that are similar to squamous cell carcinoma in situ [32].

The majority of genital warts are benign lesions, but on rare occasions, persons may develop a giant condyloma known as Buschke-Loewenstein tumor (BLT) [31, 33]. BLT is a large exo-endophytic lesion that is most often seen in persons with immunodeficiency syndromes [33]. Infection with the high-risk strains, such as HPV 16 and 18/45, may result in cervical and anorectal intraepithelial dysplasia, squamous cell carcinoma (SCC) or adenocarcinoma [34]. Pruritis is a common complaint from persons with non-cervical carcinomas resulting from HPV. Lesions may range in appearance, but tend to be irregular in shape and pigmented if visible [32].

Over time, the impact of HPV on the epidemiology of head and neck disease has become more apparent. Recurrent respiratory papillomatosis (RRP) secondary to infection with HPV types 6 or 11 may develop in infants following childbirth or persons of any age following oral sexual intercourse [8, 35]. RRP is characterized by the proliferation of multiple papillomas throughout the respiratory tract which are first detected anywhere from day one of life to 80 or more years of age [36, 37]. Juvenile onset RRP is the second most common cause of childhood hoarseness [38]. Although the lesions themselves are benign, the cumulative effect can lead to airway obstruction. Recurrences may occur following treatment and then resolve spontaneously or persist into adulthood [35, 36, 38]. Oral infections with high risk HPV

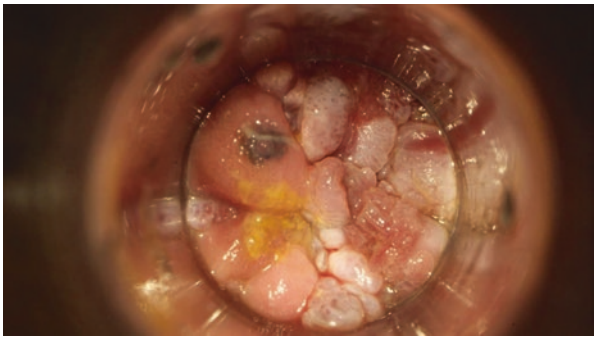

Fig. 18.1 Intra-anal condyloma visualized during high resolution anoscopy. (Courtesy of Lisa Flowers. Emory University Department of Gynecology and Obstetrics)

strains may result in head and neck squamous cell carcinoma (HNSCC) particularly on the soft palate, tonsils and the base of the tongue [39, 40].

The incubation period of HPV is unknown but ranges from 2 weeks to 18 months for genital warts, 14 months to 5 years for cellular dysplasia and up to 15 or more years for invasive cancer [34, 41–44].

Diagnostic Testing

Screening

Due to the high prevalence of HPV, women periodically undergo cytologic screening to evaluate for intraepithelial and invasive changes of the cervix secondary to HPV infection. The United States Preventive Services Task Force (USPSTF), American Cancer Society (ACS), American Society for Colposcopy and Cervical Pathology (ASCCP), American Society for Clinical Pathology (ASCP), and the American College of Obstetricians and Gynecologists (ACOG) have written consensus guidelines for cervical cancer screening. The United States Centers for Disease Control and Prevention summarizes the most recent guidelines for cervical cancer screening in average-risk women, defined as not having an immunocompromising condition such as HIV infection, or a history of in utero diethylstilbestrol exposure [45]. This begins with cytology, as outlined in Table 18.2, a summary of recommendations for cervical cancer screening in HIV-infected and uninfected women [46, 47].

The results of cytological testing dictate management and planning for follow-up screening. Cytology tests are interpreted using the Bethesda system [48–50] (Table 18.3).

Table 18.2 United States cervical cancer screening recommendations

	HIV-uninfected women	HIV-infected women
Start screening	Age 21 years regardless of risk factors	Within 1 year of onset of sexual activity but no later than 21 years of age
Frequency Age 21–29 years	Cytology every 3 years	Annually for the first 3 years. If all are normal, then cytology every 3 years
Frequency Age ≥30 years	Cytology every 3 years or Co-testing (cytology + HPV) every 5 years	Cytology every 3 years after 3 consecutive normal tests or Co-testing every 3 years if initial co-test is normal
Stop screening	Age 65 years	Never
Screening after hysterectomy	Stop for benign reasons and no history of HSIL-CIN 2+ for 20 years, otherwise routine screening for at least 20 years	Stop for benign reasons and no history of HSIL-CIN 2+, otherwise annual screening
HPV vaccinated	No change	No change

Table 18.3 Abnormal cytological results

Name	Abbreviation
Squamous cell	
Atypical squamous cells	
Of undetermined significance	ASC-US
Cannot exclude HSIL	ASC-H
Low-grade squamous intraepithelial lesion	LSIL
High-grade squamous intraepithelial lesion	HSIL
Squamous cell carcinoma	SCC
Glandular cell	
Atypical glandular cells *(endocervical, endometrial or not otherwise specified)*	
Not otherwise specified	AGC-NOS
Favor neoplastic	AGC-neoplastic
Endocervical adenocarcinoma in situ	AIS
Adenocarcinoma	

In the United States, the most frequently used liquid based cytology tests are the ThinPrep® (Hologic, Inc., Marlborough, MA) and SurePath® (Becton, Dickinson and Company, Franklin Lakes, NJ). Detection of viral nucleic acid via PCR testing is commercially available for high-risk HPV types and is an adjunctive test that may be used in women 30 years and older. The most commonly used FDA approved tests include the APTIMA® HPV 16, 18/45 Genotype Assay, and the Roche cobas® HPV Test. In most cases, women with cervical cytological abnormalities should undergo colposcopy. The exception are women between the ages of 21–24 years with ASCUS or LSIL. These women should repeat cytology testing in 1 year to evaluate for persistence. Women between ages 21–24 years who have high-grade cervical cytology (ASC-H, HSIL or AGC) or have persistent ASCUS or LSIL for 2 years should undergo colposcopy.

There are insufficient data to create national guidelines for routine anal cancer screening for men or women [51]. In 2002, the University of California San Francisco Anal Neoplasia Clinic published their screening algorithm which recommends anal cytology testing for HIV-infected men who have sex with men (MSM) annually and HIV-uninfected MSM every 2–3 years with further instructions for testing and treatment based on the grade of dysplasia detected [52]. They further recommend providers consider screening for anal cancer in all HIV-infected men and women, women with high-grade vulvar dysplasia or cervical cancer, transplant recipients and persons with anal warts [52]. If any abnormalities are noted on anal cytology, the person should be referred for high resolution anoscopy (HRA) with biopsies [47]. The New York State Department of Health AIDS Institute and the HIV Medicine Association of the Infectious Diseases Society of America have made similar recommendations for HIV-infected men and women, though other professional societies have refrained from making a statement on routine anal cancer screening [53–55].

If a person is referred to colposcopy or HRA on the basis of abnormal cytology, tissue samples are biopsied from the affected site for histological analysis. Histopathologic features suggestive of dysplasia include small blue cells (basophilic uniformly small cells), nuclear hyperchromasia (increased chromatin in cell nuclei), koilocytes (keratinocytes with a clear cytoplasm and condensed nuclei) and hypergranulosis among others [56] (Fig. 18.2a–c). In the past, multiple terminologies to describe histopathological samples from anogenital lesions existed. As a result, the Lower Anogenital Squamous Terminology (LAST) project was formed to consolidate these terms [48]. Anogenital tract lesions are graded low (LSIL) or high-grade intraepithelial lesions (HSIL) with sub-classifications using the applicable –IN subcategorization, such as cervical (CIN), vulvar (VIN), vaginal (VaIN), anal (AIN), perianal (PAIN) and penile (PeIN) intraepithelial neoplasia. Invasive lesions are differentiated into superficially invasive squamous cell carcinoma (SISCCA) or invasive squamous cell carcinoma based on the measurement (width and depth) of invasion, potential for complete surgical excision and, in the case of penile carcinoma, the presence of lymphovascular invasion (LVI) [48].

Biomarkers

Researchers are actively working to make the screening process for HPV-related cancers more objective. With the introduction of $p16^{INK4a}$ (p16) staining, pathologists have been better able to differentiate LSIL and HSIL [57]. p16 is a cyclin dependent kinase inhibitor that is significantly overexpressed in cervical intraepithelial neoplasia and invasive cancer, and is overexpressed when HPV E7 degrades pRb and cellular proliferation increases [19, 23, 57]. It then accumulates in precancerous cells and can be measured using enzyme-linked immunosorbent assays (ELISA) [57, 58]. The addition of a p16 stain to histological specimens significantly improves the reliability of diagnosing high-grade dysplasia compared with hematoxylin and eosin (H&E) morphology alone [48, 59, 60]. Another biomarker, Ki-67, indicates deregulation of the cell cycle when co-expressed with p16. The dual p16/Ki-67 stain (CINtec® PLUS, mtm Laboratories, Germany) involves a two-step immunocytochemical staining procedure on formalin-fixed, paraffin-embedded tissue specimens. Cervical or anal specimens that stain with a brown cytoplasm (p16) and red nucleus (Ki-67) are positive and favor a diagnosis of high-grade dysplasia [61–63]. p16/Ki-67 immunostaining of biopsy specimens is 90% sensitive for the diagnosis of anorectal dysplasia in HIV-infected males [64, 65].

Other biomarkers include monoclonal antibodies against two protein markers of aberrant S-phase induction, topoisomerase IIA (TOP2A) and minichromosome maintenance protein 2 (MCM2), which are commercially available as ProEx™ C (Becton, Dickinson and Company) [66]. One study demonstrated that ProEx™ C sensitivity was higher than p16/Ki-67 in predicting high-grade dysplasia when used alone, but specificity increased when combined with Ki-67 staining [67]. Studies

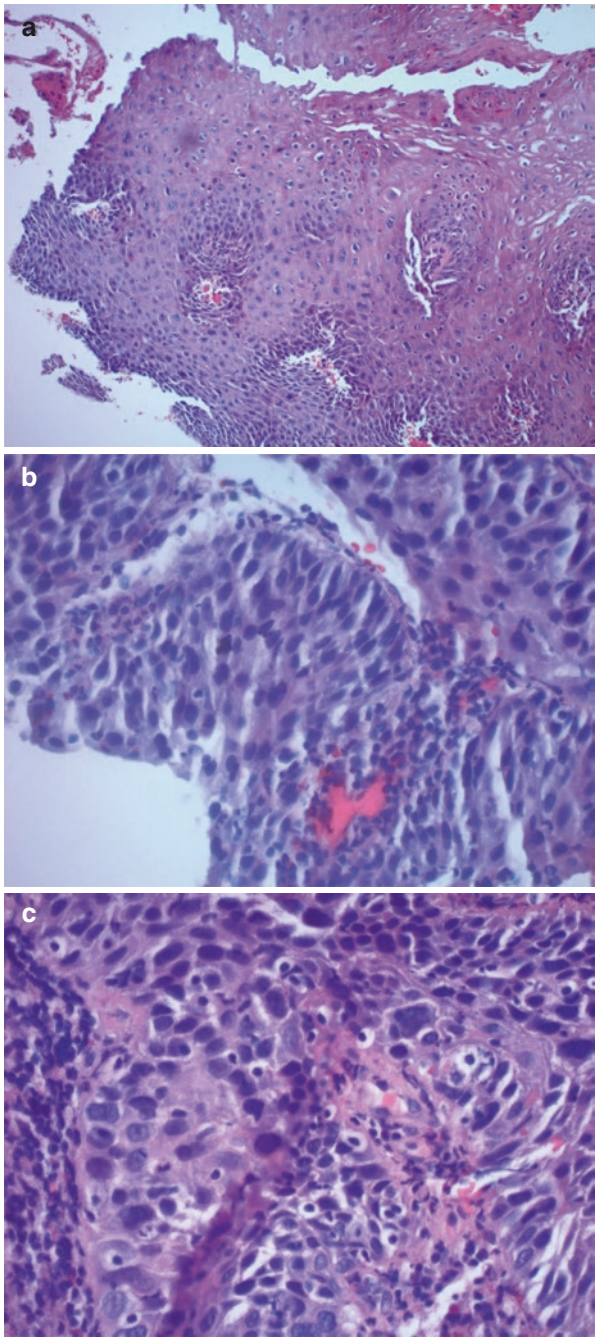

Fig. 18.2 Histopathologic Images from the Case Presentation. (**a)** Low-grade dysplasia seen in an anal histology sample displaying the presence of koilocytes. Courtesy of Mario Mosunjac. Emory University Department of Pathology. (**b)** High-grade dysplasia seen in an anal histology sample. Courtesy of Mario Mosunjac. Emory University Department of Pathology. (**c)** Nests of questionable invasion suggestive of invasive squamous cell carcinoma. (Courtesy of Mario Mosunjac. Emory University Department of Pathology)

are ongoing to evaluate the utility of cellular and viral markers as diagnostic and prognostic tools [68, 69].

Treatment

Genital Warts

Genital warts may self-resolve, but topical agents or invasive methods of treatment are often used to accelerate resolution and in cases of persistent warts. Factors to consider in treatment selection include the number of warts, morphology and size, anatomic site, cost of therapy, patient preference and anticipated adverse effects. Self-administered topical agents include imiquimod cream (Aldara), podofilox solution or gel (Condylox), or Sinecatechins ointment (Veregen) (Table 18.4). Some topical therapies require careful avoidance of application to healthy skin, which may result in pain, burning and scarring. Skin discoloration (hyper- or hypopigmentation) is another commonly reported side effect [8, 70, 71].

A trained provider may perform cryoablation with liquid nitrogen or nitrous oxide via a cryoprobe every one to 2 weeks for up to 4 months prior to or following topical therapies. Podophyllin resin 10–25% in compound tincture of benzoin applied weekly by a provider is an alternative. Trichloroacetic acid (TCA) or bichloroacetic acid (BCA) are additional provider-administered therapies which can be repeated weekly for up to 4 months. Carbon dioxide (CO2) laser ablation may be

Table 18.4 Topical therapies

Treatment	Mechanism	Dosage/Duration	Adverse effects	Contraindications
Imiquimod 3.5 or 5% cream	Stimulates interferon production	5% cream three times per week or 3.75% cream every night for up to 16 weeks	Hypopigmentation, ulcers, vesicles, can worsen autoimmune skin conditions	Avoid in pregnancy
Podofilox 0.5% solution or gel	Anti-mitotic agent that causes wart necrosis	Twice daily for 3 consecutive days per week (with 4 days of no treatment) for a maximum of 4 weeks. Daily dose should not exceed 0.5 mL	Pain at lesion site, reports of death and fetal loss with prolonged duration of application or application to broken skin	Avoid in pregnancy and during nursing
Sinecatechins 10–15% ointment	Green tea extract	0.5 cm strand three times daily for up to 16 weeks, do not wash off	Red staining, no other mucosal contact while ointment is on skin	Avoid in pregnancy, HIV, HSV or immunosuppression

used for multifocal genital warts that are not amenable to surgery [72]. Surgical removal via tangential scissor excision, shave excision, curettage, Cavitron ultrasonic surgical aspiration (CUSA) or electrosurgery (Loop electrosurgical excision procedure; LEEP) are options for persons with large numbers of genital warts or warts that are refractory to other therapies. Of note, genital warts are extremely difficult to treat and frequently recur [73, 74].

Intraepithelial Dysplasia

Providers generally elect to observe low-grade lesions (LSIL-CIN1 or AIN1) that are likely to regress, while LEEP is recommended for women with high-grade cervical lesions (HSIL-CIN2,3) [75]. Anal HSIL treatment modalities include topical imiquimod and 5-fluorouracil, TCA or BCA, cryotherapy, CO2 laser ablation, electrocautery, infrared coagulation (IRC) and surgical excision [76]. The ANCHOR study (Anal Cancer/HSIL Outcomes Research study) is a multi-center, randomized phase III trial that aims to compare the outcomes associated with topical and ablative treatment versus active monitoring for anal HSIL lesions in HIV-infected men and women [77]. Studies are ongoing to determine the safety and efficacy of therapeutic HPV vaccine candidates in treating persistent HPV infection and/or intraepithelial neoplasia [78].

Squamous Cell Carcinoma

Once SISCCA has developed, persons should undergo surgical evaluation to determine the ideal approach for removal of the lesion. If the disease has progressed to invasive SCC, an oncologist should be consulted to determine appropriate management with chemotherapy, surgery and/or radiation.

Recurrent Respiratory Papillomatosis

The current standard of care for RRP is surgical debulking of papillomas to maintain or restore airway patency [35]. Complications include burning and scarring of the larynx, stenosis and tracheoesophageal fistulae. Many persons require multiple procedures due to recurrence of lesions. In severe cases, tracheostomy may be required. Adjuvant medical therapy with acyclovir, cidofovir, or interferon may speed resolution of papillomas, though toxicity from these systemic therapies limits their use [79]. Small studies have demonstrated that intravenously administered bevacizumab (Avastin), an antibody against the anti-vascular endothelial growth factor (VEGF), may successfully treat persons with RRP [80]. Promising results

with intra-lesional cidofovir and bevacizumab have also been described in animal models and early human studies [81–83].

Prevention

The quadrivalent recombinant virus-like particle (VLP) HPV vaccine against types 6, 11, 16, 18 was licensed in 2006 under the trade name Gardasil® in the United States. A bivalent HPV 16 and 18 vaccine (2vHPV, Cervarix®, GlaxoSmithKline) was subsequently approved for use in females aged 9–25 years in 2009 by the US Food and Drug Administration, and a nonavalent vaccine (9vHPV, Gardasil 9®, Merck and Co, Inc.) was licensed in 2014 for females and males aged 9–26 years as a 3-dose series [84]. In 2014, the Strategic Advisory Group of Experts (SAGE) of the World Health Organization (WHO) recommended a 2-dose schedule of HPV vaccine with an interval of at least 6 months between doses for girls who began the series before age 15. This recommendation was based on immune-bridging studies that showed non-inferior immune response of two doses in the adolescent girls compared to three doses in the young adult women [85–87]. Further studies showed that a two-dose series was more cost-effective than the three-dose series [88]. In 2016, the Centers for Disease Control Advisory Committee for Immunization Practices (ACIP) endorsed transitioning to a 2-dose series for children <15 years of age in the United States, while maintaining the 3-dose schedule for immunocompromised persons and children who start the series on or after 15 years of age. A summary of the vaccine recommendations in the United States is listed in Table 18.5 [89]. Gardasil-9 has demonstrated efficacy of >95% for the prevention of cervical, vaginal or vulvar HSIL [89]. Studies are ongoing to determine the duration of protection from HPV vaccines, but have demonstrated sustained immunogenicity and efficacy for at least 8–10 years after vaccination to date [90, 91]. As of October 2016, Gardasil-9 is the only available HPV vaccine in the United States, though other types remain available outside of the US. Vaccine uptake has been improving over the last few years, but remains suboptimal. In 2018, the National Immunization Survey-Teen (NIS_Teen) reported that 51.1% of adolescents ages 13–17 years were up to date with their HPV vaccines. Of those, rates in females were slightly higher at 53.7% compared with males at 48.7% [92].

As of 2016, HPV vaccines were available for routine immunization in 65 countries [93]. Global rates of HPV-related disease remain high, but some countries have already demonstrated a decrease in the incidence of genital warts [94]. The incidence

Table 18.5 Vaccine recommendations in the United States

Population	Age group, y	Recommendation
Females	11–26 (may start at age 9)	Routine vaccination: 9vHPV
Males	11–21 (may start at age 9)	Routine vaccination: 9vHPV
	22–26	May receive 9vHPV
MSM and HIV+	22–26	Routine vaccination: 9vHPV

of recurrent respiratory papillomatosis has also declined following the implementation of HPV vaccination programs [95].

Special Considerations

Pregnancy

Due to lack of adequate safety studies in pregnant women, HPV vaccines are not recommended for use during pregnancy [96]. If a woman becomes pregnant after starting the series, she should delay further vaccination until the post-partum period. Of note, in trials where inadvertent vaccination with 4vHPV occurred either during or shortly before a pregnancy, there were no significant differences in adverse outcomes compared with women who remained unvaccinated [97, 98]. Secondary prevention with cytological screening is safe during pregnancy. Pregnant women with abnormal cytology may safely undergo colposcopy, but may postpone the procedure until 6 weeks post-partum in some cases. Due to possible obstetric complications, women should not undergo endocervical curettage or endometrial biopsy during pregnancy unless invasive cancer is diagnosed [75].

HIV-Infected Youth

In one cohort, HIV-infected women were more likely to develop precancerous cervical dysplasia than HIV-uninfected women when exposed to high-risk HPV strains [99]. Of note, HIV-infected female adolescents and young adults demonstrate an excellent serologic response to HPV vaccination [100, 101], but vaccine uptake rates in this population are unknown [101]. HIV-infected boys and men are also at high risk of HPV-related disease. The prevalence of anorectal HPV is as high as 32.8% in sexually active adult men [102, 103]. This number increases to 57% in the population of HIV-uninfected adult men who have sex with men (MSM) and up to 93% in HIV-infected MSM [103, 104]. HIV-infected MSM are frequently co-infected with multiple HPV types, and progress more often to anorectal dysplasia and cancer [105–107]. Of note, immune reconstitution following initiation of highly active antiretroviral therapy (HAART) does not appear to reduce the risk of HSIL [108].

Sexual Minority Populations

Risk perception among women who have sex with women (WSW) about HPV acquisition is low [109–111]. Despite lack of perceived risk, approximately 50% of WSW had an HPV infection, and >33% were infected with a high-risk HPV type in

one study [112]. The MSM population is also at high risk. A large meta-analysis showed that in the HIV-uninfected MSM population, pooled prevalence of anal HPV-16 was estimated at 12.5% (9.8–15.4) and the pooled prevalence of anal intraepithelial neoplasia was 21.5% (13.7–29.3). Anal cancer incidence was estimated at 5.1 per 100,000 [113].

Summary

HPV is ubiquitous and is the most common sexually transmitted infection in the United States. Clinical manifestations may range in severity from benign warts to invasive carcinomas. However, HPV vaccines are very efficacious in preventing infection with the most common high- and low-risk HPV strains and their complications.

Case Conclusion

In the process of preparing for possible chemotherapy and radiation therapy, multiple additional diagnostic and staging biopsies were obtained. The highest-grade disease detected subsequently was LSIL-AIN1. The patient was monitored closely without further therapy over the following years. Three years later, he continued to have difficulty with anal strictures and fissures, but had no further symptoms or signs concerning for malignancy.

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Chapter 19
Sexually Transmitted Diseases in Adolescents: Viral Hepatitis

Aley G. Kalapila and Shireesha Dhanireddy

Case

A 19 year HIV-positive patient comes for a routine follow up visit. Six months prior, he established care following a diagnosis of acute HIV infection. Since then, he has been fully adherent to his antiretroviral therapy (ART) and achieved viral suppression of HIV, with a subsequent rise in CD4+ T-cell count to 655 cells/mm^3 from a baseline of 425 cells/mm^3. Other baseline labs drawn at the time of his initial HIV diagnosis indicate immunity against hepatitis A and hepatitis B (surface antibody (sAb) and core antibody (cAb) positive) and negative hepatitis C (HCV) serology. During this clinic visit, he denies any complaints and says that he feels well. Upon questioning, he endorses multiple recent unprotected sexual encounters with different partners. He states that he has sex with men exclusively, and reports engaging in oral as well as both receptive and insertive anal intercourse. Vital signs and physical exam are within normal limits. Routine blood work is obtained, including a rapid plasma reagin (RPR) test for syphilis, as well as anal/throat swabs and urine nucleic acid amplification testing for gonorrhea and chlamydia. His laboratory work-up is notable for new mild elevation of his aspartate aminotransferase (AST) and alanine aminotransferase (ALT), approximately 1.5–2 times the upper limit of normal. Bilirubin, renal function, and complete blood count (CBC) are

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unremarkable, syphilis, gonorrhea and chlamydia testing is negative, HIV viral load is undetectable and his CD4+ T-cell count is stable. He is advised to return to clinic for further testing, which reveals similarly abnormal liver function tests as before, and a newly positive hepatitis C antibody test with a viral load (HCV RNA) of six million copies/mL.

Questions:

- What are the features of acute hepatitis C infection?
- What (if any) treatment is indicated at this time?
- How should the patient be counseled to avoid further transmission?
- What other testing is important when a diagnosis of sexually transmitted hepatitis C infection is made?

Epidemiology

In any textbook of sexually transmitted infections, hepatitis B virus (HBV) has long been considered a stalwart, especially in developing countries where prevalence is high, perinatal transmission prevails and vaccination rates lag behind the United States (US). However, within the last decade or so, there is burgeoning epidemiologic and molecular data that shed light on the sexual transmission of hepatitis A virus (HAV) and hepatitis C virus (HCV) infection, specifically in certain high-risk patient populations.

HAV, an RNA virus, has traditionally been known as a foodborne illness transmitted via the consumption of fecally contaminated food and water. In countries where poverty prohibits adequate sanitation and/or access to clean, potable water, HAV is often endemic. In the US, by contrast, fewer HAV infections are transmitted via this conventional route. A CDC surveillance report of hepatitis A cases in 2010 identified specific risk information associated with the infection in only 25% of cases. Aside from more traditional risk factors such as international travel, or food/water exposure, sexual contact particularly amongst men who have sex with men (MSM) is also increasingly recognized as a route of transmission [1, 2]. Furthermore, there have been multiple outbreaks of sexually transmitted HAV infection among MSM in Europe, Japan, Australia and North America [3–6]. Practices that have been associated with the sexual transmission of HAV include oral-anal contact, digital to anal contact, and insertive anal intercourse [5]. On the other hand, scientific data are lacking supporting transmission of HAV via heterosexual contact [5, 7].

Unlike HAV, there is extensive biological data demonstrating presence of hepatitis B virus (HBV) DNA in a variety of media including mucosal surfaces, semen, menstrual blood, rectal mucosa, vaginal discharge, and the anal canal, among others, illustrating that HBV can be efficiently transmitted sexually [5]. Between 8% and 28% of acute HBV cases in the US in 2010 were associated with defined risk factors including 2 or more sexual partners, male-male sexual contact, and/or sexual activity with a known or suspected HBV-infected person [1]. Additionally, data point toward higher seroprevalence of HBV among MSM relative to heterosexual populations. An anonymous, cross-sectional survey of over 3000 MSM in the US

between the ages of 15 and 22 years, during 1994–1998, known as the Young Men's Survey, collected information on prior HBV infection defined as a presence of anti-hepatitis core antibody (HBcAb) and current HBV infection indicated with a positive HBV surface antigen (HBsAg). Rates ranged from 2% in 15 year olds to around 17% in 22 year olds. Data from the subsequent survey (1998–2000) found approximately 21% of 2800 MSM (aged 23–29 years) had seromarkers of HBV infection [8].

HBV can also be transmitted perinatally; this happens more commonly outside the US. Epidemiologic data regarding prevalence of HBV infection among immigrant children is largely unknown. While the impact of immigration on the magnitude of disease burden of acute and chronic HBV in children/adolescents is not well delineated in the US, there is no doubt that these have public health ramifications, particularly in light of the ongoing refugee & migrant crisis [9].

Following initial exposure, HBV can either cause acute or chronic infection, with roughly 25% of the latter developing cirrhosis and/or hepatocellular carcinoma [9]. Furthermore, perinatal vertical transmission can lead to chronic liver disease in children. In an effort to reduce the burden of morbidity and mortality related to longstanding HBV infection, the CDC has recommended universal HBV vaccination for all newborns since the 1990s. Vaccination is also recommended for high risk populations including MSM, and other at-risk groups such as commercial sex workers or individuals with multiple sexual partners or recent STD diagnosis [10].

Amongst all age-groups, the anticipated aftermath of a steady decline in chronic HBV infection in the US with the implementation of the universal HBV vaccination strategy has been offset by the ongoing migration of HBV infected individuals from endemic countries. As a result, the epidemiology remains dynamic, but the best, most recent data for adolescents, comes from the National Health and Nutrition Examination Survey (NHANES) which estimated prevalence of chronic HBV infection in the US for three time periods: 1988–1994 (21,260 persons); 1998–2008 (29,828 persons); 2007–2012 (22,358 persons). Furthermore, for 2007–2012, NHANES oversampled non-Hispanic Asians, an ethnic group considered to have the highest prevalence of HBV infection in the US. The NHANES adjusted prevalence of chronic HBV for individuals under the age of 20 declined from 0.2% in 1998–2008 to 0.03% in 2007–2012, although the latter estimate was based on only 3 positive sample cases and must be interpreted with caution [11].

Hepatitis C is a common cause of viral hepatitis and a blood borne pathogen, affecting approximately three million Americans, mostly individuals born between 1945 and 65, commonly referred to as the "baby-boomers". For the US adolescent population, NHANES data from 2003 to 2010 estimates a chronic HCV prevalence rate of 0.4% in the 12–19 year old age group [12, 13]. While the bulk of these infections occurred via percutaneous exposure, there is now a widely accepted, clinically relevant body of literature on sexual transmission of HCV in MSM, especially those who practice unprotected anal intercourse [14]. Studies among HCV serodiscordant heterosexual couples suggest extremely inefficient, though not neglible transmission [15]. Analysis of multiple clusters of HCV outbreaks in the MSM population, have identified several key factors associated with sexual transmission of HCV including HIV co-infection, simultaneous drug use, concomitant STDs, especially ulcerative infections such as lymphogranuloma venereum (LGV), syphilis or herpes

simplex virus (HSV) proctitis, unprotected anal intercourse with higher risk for the receptive partner, multiple sex partners and/or the use of sex toys or other practices (such as fisting) which facilitate mucosal damage and bleeding [5, 16–19].

Microbiology and Pathophysiology

Transmission of HAV infection, including sexual transmission, occurs exclusively as a result of ingestion, typically via the fecal-oral route. HAV is a small, non-enveloped RNA virus that, following ingestion, makes its way to the liver, where it replicates exclusively in the hepatocyte cytoplasm. Next, it is excreted into bile and eventually, shed in high concentrations in the feces. The incubation period tends to last between 2 and 6 weeks [5]. Clinical presentation of HAV infection is often a self-limited illness without progression to a chronic liver disease. Although rare, acute liver failure due to HAV can occur. The risk, frequency and severity of symptoms from this infection directly correlate with advancing age, with younger patients, especially those below age 5 years having asymptomatic infection [20]. Symptoms, including jaundice, nausea, and malaise, typically last for approximately 2 weeks with resolution. Atypical extra-hepatic manifestations include leukocytoclastic vasculitis, cryoglobulinemia, glomerulonephritis, arthritis, and immune complex mediated disease [21]. The hepatotoxic injury associated with this disease process has been attributed to the host immune responses to HAV, specifically mediated by HAV specific cytotoxic CD8+ T cell and natural killer cells. Consequently, an intense host immune response leading to rapid reduction of circulating HAV RNA, also leads to a severe hepatitis presentation. Interferon gamma is also believed to play a key role in facilitating clearance of infected hepatocytes [22, 23]. HAV IgG specific antibodies, that are borne of HAV infection, confer lifelong immunity against re-infection [5].

Hepatitis B is a small (3.4 kilobase) DNA virus, belonging to the hepadnaviridae family. The DNA genome of HBV consists of four overlapping open reading frames (ORFs) that encode several proteins: envelope (pre-S/S) proteins, core nucleocapsid protein and e antigen, polymerase proteins, and X proteins. The envelope proteins (HBsAg), as the name implies, form the viral envelope. The core protein antigen, (HBcAg), encloses HBV DNA. The e antigen (HBeAg) is an indicator of active viral replication, which because of its ability to manipulate immune responses to HBV, often contributes to viral persistence and hence the establishment of chronic infection. Finally, the X proteins are potent transcriptional transactivators that assist with viral replication and possibly carcinogenesis [24].

Virus particles first attach onto hepatocytes, after which uncoating occurs in the cytoplasm followed by entry of the viral genome into the hepatocyte nucleus. Initially during the replication cycle, the HBV genome is initially converted from a relaxed circular, partially ds DNA to a stable covalently closed circular DNA (cccDNA). This cccDNA is a stable replicative intermediate, and persists as episomal material, and are critical to the difficulty of viral clearance due to its long

half-life. The rest of the replication occurs via RNA intermediates using reverse transcription [24].

The pathophysiology of HBV is complicated and not fully understood. In fact, much of the virus replication strategy operates in a "stealth mode" so as to evade the innate immune system. Although the specific mechanisms of how this occurs have not been fully elucidated, several hypotheses have been proposed such as an attenuated T cell response to viral replication or up-regulation of cytokine, interleukin-10, which has anti-inflammatory and immunosuppressive properties [24–27]. Acute HBV infection tends to be mostly asymptomatic. Chronic infection, characterized by active liver inflammation, fibrosis and cirrhosis, exhibits a spectrum of pathophysiology defined by level of HBV viremia, aminotransferase elevations as a marker of hepatic necrosis and HBeAg status. Resolution of infection relies on CD4+ and CD8+ T lymphocytes as well natural killer cells. Viral persistence, however, is associated with immune failure and predisposes the affected individual to developing hepatocellular carcinoma and/or cirrhosis [25].

Hepatitis C is a positive sense, single stranded RNA virus, belonging to the *Flaviviridae* family. Hepatocytes are the natural targets of HCV, although viral entry and replication are not fully understood. Acute infection is often asymptomatic, but may occasionally be associated with non-specific flu-like symptoms and a subtle aminotransferase elevation. Spontaneous viral clearance, which occurs in approximately 15–45% of individuals, relies on viral factors and host CD4+ and CD8+ T cell responses, and usually occurs within 6–12 months after initial infection [16]. The HCV RNA dependent RNA polymerase, is the key replicative enzyme. It lacks proof-reading abilities, thus generating a large number of genetically diverse, mutant 'quasispecies virions' (10^{10}–10^{12} per day). This burden of viremia can overwhelm the host immunity, leading to chronic infection. The subsequent liver fibrosis can progress to cirrhosis over decades, although this evolution can be expedited by other hepatic insults such as concomitant HBV or HIV infection, alcoholic liver disease or steatohepatitis [16, 28, 29].

Diagnosis and Screening

Definitive diagnosis of acute HAV infection is made with the appropriate combination of clinical and biochemical features as well as serological confirmation of HAV specific IgM antibodies [20]. Routine screening for HAV infection in adolescents is usually not recommended unless the individual is exhibiting symptoms, although it is not unusual for serologies to be obtained in primary care settings to verify immunity [20].

Diagnosis of prior HBV infection, ongoing acute versus chronic infection or immunity against HBV is determined by interpreting the results of a combination serological markers, specifically HBV antigens and antibodies, and HBV DNA levels using PCR [20]. The hallmark of active HBV infection, both acute and chronic, is marked by the presence of Hepatitis B surface antigen (HBsAg). As HBsAg

clears, hepatitis surface antibody (HBsAb) levels usually start to rise demonstrating resolution of infection. The hepatitis B core antibody (HBcAb) can be a marker of acute, chronic or prior infection. Typically, IgM HBcAbs are found during acute HBV infection. IgG HBcAb, however, indicate either a resolved acute infection or chronic infection. Most US-based lab testing, measure total and IgM HBcAb levels. Hence, when trying to distinguish acute from chronic infection, IgM and total HBcAb levels should be checked along with simultaneous testing for HBsAg and HBsAb. The surface antigen/antibody and core antibody results form the backbone of HBV diagnosis [20]. The diagnostic algorithm to interpret HBV serologies is indicated in Table 19.1.

Other relevant HBV diagnostics include the hepatitis B e antigen (HBeAg) which signals active viral replication and is associated with substantial HBV viremia. Waning levels of HBeAg and increasing levels of Hepatitis B e Antibody (HBeAb) are usually associated with remission of HBV DNA replication, declining HBV viremia and attenuated liver disease [20, 30, 31].

Finally, HBV DNA PCR results are used to verify the presence of active HBV replication as well as to determine need for and response to antiviral treatment [32].

Testing of adolescents for asymptomatic HBV infection, much like HAV and HCV, is primarily indicated in individuals who are at increased risk for acquiring the disease including injection drug users, HIV positive persons, those with multiple sexual partners or those born in countries where HBV is endemic. Additionally, all pregnant women warrant screening for HBV as soon as they engage with prenatal care, both to immunize those who do not have infection and to prevent perinatal transmission for those with chronic disease. Further guidance on monitoring and management of chronic HBV in pregnancy can be found in the updated AASLD guidelines [32].

A serologic assay for antibodies against Hepatitis C is the recommended first line diagnostic test for active HCV infection. This ELISA-based test, approved by the FDA, detects antibodies against specific viral proteins and is reported as either positive

Table 19.1 HBV serology interpretation

	Serological markers			
	HBsAg	HBsAb	Total HBcAb	IgM HBcAb
Interpretation				
Early acute infection	+	−	−	−
Acute infection	+	−	+	+
Resolved infection with subsequent immunity	−	+	+	−
Chronic infection	+	−	+	−
Vaccinated (no prior infection)	−	+	−	−
False positive OR Past infection OR Chronic occult infection	−	−	+	−

Adapted from CDCSTD Treatment guidelines; Accessed November 2016 [20]

or negative. A positive test indicates that at some point, the individual was exposed to HCV. The test does not differentiate between resolved versus ongoing infection. With its high specificity and sensitivity, the HCV serology is an excellent screening tool. In order to determine the presence of active infection in the setting of a positive HCV Ab test, either a qualitative or quantitative HCV RNA is performed. Further testing beyond this point is indicated if the decision is made to pursue treatment for HCV, in which case, a genotype test will help guide selection of appropriate therapeutic antivirals. Of importance when counseling individuals with resolved HCV infection regarding transmission, the presence of HCV Abs does not confer immunity against re-infection. As such, risk factor modification should be addressed in order to minimize potential for re-infection [16, 33].

Routine adolescent screening for HCV infection is not indicated unless they belong to high risk groups including HIV positive men who have sex with men or injection drug users or siblings of children with perinatally acquired chronic HCV. However, due to more HCV infections in young adults, including women of childbearing age, the AASLD has updated its HCV management guidelines to include screening of all pregnant women at the initial prenatal visit so as to assess liver disease as well as facilitate linkage to HCV care post-partum [34]. Current data does not seem to indicate a negative impact on pregnancy from HCV infection, although pregnant women are at increased risk for intrahepatic cholestasis of pregnancy. Additional details on lab monitoring and management of HCV in pregnancy can be found on the AASLD treatment guidelines website (www.hcvguidelines.org).

Treatment

As previously mentioned, disease caused by HAV is overwhelmingly self-limited, with more severe presentations associated with older age and/or comorbid chronic liver disease. As such, the treatment of this illness relies on supportive measures, with an effort to prevent further hepatotoxic injury and subsequent acute liver failure. In this context, medicines that rely on hepatic metabolism (acetaminophen, opiates, benzodiazepines for example) should be avoided [20].

Similar to HAV, supportive care is the recommended treatment for acute HBV infection. In some instances, acute HBV can have a fulminant course leading to consideration of orthotopic liver transplant. Chronic hepatitis B, however, is more complicated. There are several therapeutic antivirals available that can suppress viral replication and abate liver disease. Indication for use of these drugs is variable, relying on a host of factors such as race, level of viremia and co-infection with HIV. Furthermore, depending on the extent of chronic liver disease, additional management, beyond antivirals, may be warranted such as screening for hepatocellular carcinoma. In the case of pregnancy, it is unusual for young women to exhibit signs of active liver inflammation in the setting of chronic HBV infection. Hence, the current AASLD guidelines do not recommend antiviral treatment due to concerns for adverse fetal outcomes especially early on in pregnancy, during organogenesis. In

general, these women should be co-managed by high-risk obstetrics and an infectious disease or hepatology specialist. Antivirals may be indicated for pregnant women with elevated viremia or liver inflammation. Regardless, in all such scenarios, it is best to refer to a specialist for antiviral treatment of HBV. Further details can be found by referring to practice guidelines from the American Association for the Study of Liver Diseases regarding the treatment of chronic hepatitis B [32].

Approximately 15–45% of individuals with acute HCV will resolve their infections spontaneously. For those that develop chronic infection, determining genotype helps guide selection of appropriate therapeutics. Unlike HIV and HBV, HCV has no stable genetic reservoir of DNA. The HCV RNA particles have a half-life of approximately 3–4 hours. Therefore, by preventing viral replication, HCV genetic material can be eradicated, leading to cure. As such, the approach to treatment of HCV has fundamentally changed over the last decade. With the introduction of directly acting antiviral agents (DAAs), HCV treatment has moved from immunomodulatory agents to almost exclusively using drugs that inhibit viral replication. By shifting the central approach to treatment of HCV toward attacking the virus, the therapeutics have become significantly more effective and better tolerated, with fewer adverse effects, compared to the interferon-alpha-based therapies.

The replication mechanics of HCV require at least 2 drugs acting at different parts of the viral life cycle. The data on safety of DAAs in the pediatric and adolescent population continue to evolve. As of the time of this chapter writing, DAAs that are approved are recommended for children and adolescents, 3 years of age or older. Treatment of HCV should be deferred to an expert. More details can be found by referring to the AASLD and Infectious Diseases Society of America (IDSA) practice guidelines for testing, managing and treating hepatitis C (www.hcvguidelines.org).

Prevention

Vaccinations lay the groundwork for prevention of HAV and HBV infection in the United States (US). HAV vaccines are highly effective and are now recommended as part of the routine immunization schedule for pediatrics patients (http://www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/hepa.html). Currently, in the US, there are two monovalent HAV vaccines, consisting of inactivated Hepatitis A antigen purified from cell culture. They have both been approved by the Federal Drug Administration (FDA) for children ≥12 months – HAVRIX, GlaxoSmithKline; and VAQTA, Merck and Co., Inc. Vaccination before 12 months is not recommended to avoid interfering with passively acquired maternal antibodies. Typically, either of these should be administered intramuscularly using a 2 dose schedule, at least 6–18 months apart. The HAV vaccines have impeccable safety records and excellent immunogenicity. Through the federally funded Vaccines for Children Program, children and adolescents <19 years of age have access to the HAV vaccines [20, 21]. Due to the risk of HAV in the MSM population in the US, Advisory Committee on

Immunization Practices (ACIP) recommends immunization of all MSM against HAV. As of the mid-1990s in the US, vaccination schedules have now adopted universal vaccination for all infants, with subsequent decrease in acute infections across all age groups [35].

Twinrix, a combination HAV and HBV vaccine is licensed for use in the US for adults >18 years, not previously immunized, who are at risk for acquiring HAV or HBV infections. This is administered in 3 doses at 0, 1 and 6 months and is just as effective at inducing protective antibody responses as their monovalent counterparts.

For HBV, there are currently three recombinant vaccines available in the US for children and adolescents. Two of these, Recombivax and Engerix B, are monovalent vaccines, approved for all age groups and are pertinent to this discussion on adolescent health. Twinrix, the combination HAV/HBV vaccine is discussed above and is indicated in individuals older than 18 years of age [20]. In November 2017, the FDA approved a new HBV vaccine for adults 18 years and older. Heplisav-B, combines an yeast-derived recombinant HBsAg with a novel immunostimulatory adjuvant which directs the host immune system to mount a response to the HBsAg. It should be administered in 2 doses, given 1 month apart but currently, is not indicated in pregnant adults [36].

The dosing and administration schedule for Recombivax and Engerix B vaccines depend on the age of the recipient, and the adolescent immunization schedule is indicated below in Table 19.2.

At this time, in the US, immunization against HBV is recommended for all infants. Catch-up immunization is also recommended for all unvaccinated children and adolescents, especially those at higher risk. Risk factors include (but are not limited to): injection drug use, high risk sexual behaviors, those born in countries or to parents from countries with high prevalence of HBV infection, those in the same household as other individuals from HBV-endemic countries, individuals receiving chronic hemodialysis, those with chronic liver disease, and sexual partners of HBsAg positive individuals [37, 38]. Pre-vaccination serologic testing, specifically

Table 19.2 HBV vaccination schedule for adolescents

Age group	Administration schedule			Vaccine, dose (μg), volume (mL)
	0	1–2 months	4–6 months	
11–19 years	X	X	X	Recombivax HB, 5 μg, 0.5 mL
	X	X	X	Engerix B, 10 μg, 0.5 mL
11–15 years	X		X	Recombivax HB, 10 μg, 1 mL
Hemodialysis and other immunocompromised persons <20 years	X	X	X	Recombivax HB, 5 μg, 0.5 mL
	X	X	X	Engerix B, 10 μg, 0.5 mL

Adapted from STD Treatment guidelines; Accessed November 2016 [20]

HBcAb, should be checked in these high risk cases, with subsequent testing of HBsAg in persons with positive HBcAb, to ensure the individual does not have evidence of active HBV infection [38]. Post- vaccination serologies are not routinely recommended to verify immunity, unless the person is immunocompromised, including HIV infection, or those with direct mucosal or blood exposure to HBsAg positive sources (eg: sex partners) [20].

Finally, post-exposure prophylaxis (PEP) is also an important mode of HBV prevention. In previously unvaccinated individuals, HBIG is typically administered following a concerning exposure to a known HBsAg positive source, as an adjunct followed by HBV vaccination. This immune prophylaxis has most benefit when done within 24 h of exposure and for up to 7d for a percutaneous and 14d for a sexual exposure. The HBV immunization series should be completely administered. In those individuals who have received HBV vaccination in the past, only a known percutaneous or blood exposure to a HBsAg positive individual warrants just the HBV vaccine booster dose [20].

In contrast to HAV and HBV, there is no vaccine to prevent HCV infection. Thus, prevention efforts rest on transmission counseling which primarily entails addressing high risk behaviors with patients. There is also evidence indicating that concurrent ulcerative STIs, such as LGV or HSV proctitis or syphilis, can facilitate sexual transmission of HCV among MSM [19, 39–42]. Consequently, frank discussions with patients regarding sexual behaviors and drug use practices as well as screening of high risk individuals with as needed treatment of these STIs will also help attenuate sexual transmission of HCV [5].

Case Conclusion

Clinically, acute HCV infection can often be hard to diagnose due to the relative paucity of symptoms. Typically, most individuals tend to be asymptomatic, although some mild non-specific symptoms may be present suggestive of hepatic injury such as fatigue, nausea, right upper quadrant tenderness or jaundice. Regardless, transaminitis is typically present, although these derangements may be subtle as described in the case above. As such, a high degree of suspicion in the appropriate clinical context – in this case a young man engaging in receptive anal intercourse with unknown partners - is needed in order to make the diagnosis.

Approximately 15–25% of patients with acute HCV will spontaneously clear HCV. Although, it is important to note that this proportion is smaller in HIV co-infected patients. Regardless, it is appropriate to wait at least 3–6 months, in order to determine if this patient will spontaneously clear his HCV infection. A persistently detectable HCV RNA after 6 months suggests chronic HCV infection and the decision can be made to pursue further treatment, according to the American Association of the Study of Liver Diseases (AASLD) guidelines. Therefore, no treatment is indicated at this time for this patient.

If the patient does not spontaneously clear HCV, treatment should be considered. Unlike the days of interferon therapy, the new directly acting antiviral (DAA) medications for treatment of HCV have greatly simplified the ability to treat patients for HCV. Even with those individuals co-infected with HIV, the HCV DAAs are associated with high cure rates, thus diminishing the urgency to treat acute HCV infections.

Multiple longitudinal studies have demonstrated increased risk (adjusted odds ratio 4.1–5.7) of sexually acquired HCV in HIV-infected MSM compared to HIV-uninfected MSM [17–19, 43]. Thus, in depth STD counseling is necessary in this case scenario, to further prevent transmission of HCV to uninfected persons. Other pertinent testing, includes looking for other STDs as well as also checking an HCV genotype if the decision is made to pursue DAA treatment.

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