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Amy Lynn Clouse
Jo Ann Woodward *Editors*

Sexually Transmitted Diseases

A Practical Guide for Primary Care

Second Edition

Humana Press

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Preface

A valuable approach to providing excellent care of patients with sexually transmitted diseases requires that primary care physicians integrate detailed knowledge and clinical wisdom along with empathy to provide care of patients for one of the most emotionally difficult diseases any person encounters during his or her lifetime. STDs are common; they account for 5 % of all outpatient office visits in the United States, and are primarily managed by family doctors, internists, obstetrician-gynecologists, emergency room physicians, primary care nurse practitioners, and physician assistants. Four of the top five reportable infectious diseases in the United States are STDs [1]. In fact, one in ten Americans will have an STD at some time during his or her life [2]. STDs are unique in that they are defined not by their symptoms, or by the body organs that they infect, or by the microorganisms that cause infection, but rather by their mode of transmission—primarily through sexual intercourse. While STDs are related through their mode of transmission, they are heterogeneous and their effects on the body, causing illness that ranges from limited, localized, and asymptomatic disease to serious systemic acute and chronic illness.

STDs reflect the intersection of public health with private decision making and the actions and consequences that ensue from those decisions. Because of their mode of transmission, and the fact that what is inherently a private activity has direct public health consequences, prevention, screening, and treatment of STDs must occur as a part of public discourse as well as private discussions between clinicians and their patients. Unlike most other diseases and infections, the diagnosis of an STD often carries with it a stigma of guilt and embarrassment. This can make the discussion about the mode of acquisition and future prevention difficult for patients and practitioners, resulting in less than optimal communication, misinformation, increased psychosocial burden and the risk of increased disease transmission into the future.

Discussing sexual behavior can be an embarrassing experience that is often avoided by the patient and the practitioner. We as practitioners carry certain biases, recognized or not. These are obvious obstacles to excellent care. The practitioner's approach, however, can change the experience of a patient from embarrassing or even shameful into an opportunity to empower themselves with knowledge and

behavioral change that may save their life. STDs should be handled candidly and honestly, with empathy for the psychosocial ramifications of the illness and an eye toward the possibility of personal growth and modifications of behavior.

The history of STDs is informative. STDs were long ago recognized as being spread by sexual contact, and where therefore referred to as "*venereal diseases*," named after the Greek goddess of love, Venus. Individuals who had syphilis were shunned. Until the 1960s, syphilis and gonorrhea were the only STDs. During the 1970s Chlamydia trachomatis became recognized as causing urethritis, cervicitis, and pelvic inflammatory disease (PID). During the 1980s, HSV-2 appeared to be almost epidemic, and was in fact thought, incorrectly, to be the etiologic agent for cervical cancer. Also during the 1980s the acquired immunodeficiency virus (AIDS) was identified with the human immunodeficiency virus (HIV) being identified as the etiologic agent. During the early part of the AIDS epidemic, paralleling the history of the syphilis epidemic, biases against groups felt to transmit the virus were common [3]. In the latter part of the 1980s and 1990s the role of the sexually transmitted Human Papilloma Virus (HPV) in the development of cervical cancer was recognized, culminating in the development of HPV vaccine, the first vaccine thought to prevent the development of cancer [2].

STDs in the United States continue to be an important public health challenge. There were over 1.3 million cases of chlamydia infections reported in 2010, for a rate of 426.0 per 100,000 population, which represents the highest rate of any infection reportable to the CDC and was a 5.1 % increase compared to the previous year. Chlamydia infections are usually asymptomatic in women but can lead to PID and subsequent infertility, ectopic pregnancy, and chronic pelvic pain. Rates in women were more than twice that of men in 2010, partially due to the increased rates of screening. Racial and ethnic disparities were clear; the chlamydia rate in blacks was 8 times that in whites [1].

In contrast to chlamydia, gonorrhea infection reached its lowest rate ever in 2009. Rates dropped to 98.1 per 100,000 from a high of over 464 per 100,000 population in 1975. 2010 saw a slight increase to 100.8 per 100,000 population. Gonorrhea is a significant cause of PID but, despite the overall decline in infection rates, treatment is becoming more difficult. The *Gonococcal Isolate Surveillance Project* from the CDC in 2012 showed increasing gonococcal resistance to cephalosporins, to the point where oral cephalosporins are no longer recommended as treatment [4].

The rate of reported primary and secondary syphilis in the United States was at an historic low of approximately 11 per 100,000 between 2000 and 2005. A concerning trend, however, has developed recently with the rate climbing by over one-third to 14.9 per 100,00 in 2010, most marked in men who have sex with men.

As mentioned above, new technology is emerging with the most important example being the human papillomavirus vaccine and the probability of decreased development of cervical cancer. The CDC's Advisory Committee on Immunization Practices (ACIP) in 2006 recommended vaccination of girls starting at age 11–12, and in 2011 recommended routine vaccination of males age 11–12.

Addressing STDs adequately requires individual practitioners with a detailed understanding of STDs to see patients with both knowledge and empathy as a primary directive, as well as a public health approach for disease surveillance, detection, and treatment. Working to eliminate the stigma of STDs by engaging in frank discussions about symptoms and sexual behavior, screening for appropriate STDs in the appropriate setting, and continuing to profess the message of responsible sexual decision making puts primary care physicians in a unique position to carry out prevention, detection, and treatment of sexually transmitted diseases.

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A book can be like a wild flower caught out of the corner of one's eye while walking down a winding path. What begins as a surprise takes form as one looks more closely. Then as astonishment shifts to appreciation it can take one on an unanticipated journey. In that way, a book is like life, never certain, but filled with unanticipated challenges that have to be reckoned with through patience and cooperation with others. This book on sexually transmitted diseases came upon us as such a surprise and we have learned many things in the course of its writing. One of the things that we, the editors, learned again was how fortunate we are to work in an environment where learners of all levels—medical students, residents, and attending physicians—work together to provide excellent care for patients, and how we are able to combine the joys and challenges of patient care with the intellectual excitement of putting information together, in this case in the form of a book.

In writing this book, Amy and Neil are reminded of our good fortune to be working with smart, fun, inquisitive, supportive colleagues—Mat Clark, Adam Chrusch, Trip Hansen, Natalie McGann, John Russell, and Meera Shah. We have together, along with the support of many team players including Joyce Westaby and Muriel Wimpenny, been able to develop a family medicine residency program that integrates the best aspects of clinical and academic medicine in an outstanding and enjoyable manner. A residency program like this, that sees patients from all backgrounds regardless of their ability to pay in an environment of support and respect, can only occur when supported strongly by a parent hospital and the people who are in charge of that hospital—Larry Merlis, Jack Kelly, Meg McGoldrick, and many others—all of whom share a commitment to doing the right thing—providing high quality, safe, compassionate medical care to the patients in our community.

The joys of life, whether it is writing a book or spotting a wild flower during a walk, have much less meaning when they are not shared. We feel lucky to be able to share our appreciation and thanks with both our professional and our personal families. Our professional families are mentioned above. Our personal families follow. Neil's appreciation goes to Alison, Aaron, and Ava each of whom know they hold a special wild place in his heart. Amy's appreciation goes to her family and friends who continue to remind her to live with grace and take herself a little less seriously,

seriously. Jo Ann's appreciation is given to Linda Caryn Goldman and the multidisciplinary team approach that this book reflects. Representing different disciplines of healthcare providers is part of the integrative nature of this book.

We hope that you find this book useful and informative.

Jenkintown, PA, USA — Neil S. Skolnik
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Chapter 1
Human Papillomavirus and Genital Warts

Linda Caryn Goldman and Amy Lynn Clouse

Introduction

Unknown until the second half of the twentieth century, human papillomavirus (HPV) is now recognized as being one of the most common sexually transmitted infections (STI) in the United States, accounting for more than one third of the new cases of STIs each year [1]. Most HPV infections cause no symptoms, other types can cause genital warts, and still others cause invasive squamous cell anogenital carcinoma. This chapter provides an overview of HPV infection—its transmissibility and epidemiology. It focuses on genital warts in its discussion of the clinical consequences of HPV infection and treatment options. The contribution HPV infection makes to various genital cancers is mentioned, but the screening, diagnosis, and treatments of these conditions are outside the scope of this book.

Prevalence/Incidence

Precise estimates of the incidence of HPV infection are not available for several reasons. First, HPV is not a reportable disease. Additionally, most infections are subclinical. Of the patients who develop findings with HPV infection, most have

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only indirect indication of infections, such as abnormal cervical cytology. In patients who have more obvious manifestations of infection, such as external genital warts, no formal testing is done to document the presence of HPV. Finally, HPV also causes recurrent outbreaks of lesions. Because most first infections are asymptomatic, it may be difficult to recognize new cases from recurrent infections, which must be done to calculate incidence.

Prevalence of HPV infection is also difficult to estimate. The usual technique used to estimate the number of people infected with HPV is to measure serum antibodies. However, most people who acquire the viral infection clear that infection within 1–2 years; others may harbor the infection for years without outbreaks; others will have obvious recurrences. Some people in these groups will have positive antibody titers, so that antibodies may overstate the number of people who are currently infected (prevalence) [2]. Confusing the situation even further is the fact that only 50 % of individuals infected with HPV will develop detectable antibody titers to the virus, which could underestimate prevalence.

Despite these limitations, several studies performed over the past 20 years have demonstrated a steady rise in the number of new cases of genital HPV. The number of office visits for genital HPV disease has increased over the last 30 years [3]. It has been estimated that about 15 % (20–24 million) of adults in the United States are currently infected with this virus; 9.2 million of them are between the ages of 15 and 24 years [4–6]. The prevalence of HPV infection among sexually active college women over a 3-year period has been reported to be over 40 %; the greatest prevalence is among women with 3 or more lifetime partners or partners with 2 or more lifetime sexual partners [7–9].

Risk Factors

Acquisition of HPV is clearly related to sexual activity. The highest risk groups for new infection are sexually active adolescents under the age of 19, followed by adults aged 19–30 [10]. The risk of HPV infection increases with number of lifetime sex partners. In one study, patients with 10 or more partners were found to have 58 % current infection rates compared with an 8 % rate in those with zero or one partner [11]. Risk factors for HPV acquisition are similar to those for other STIs, and include multiple recent sex partners and changing sex partners in the last year. Coinfection with other STDs and early age at first intercourse increase the risk of HPV infection. Expression of the virus and clearance of viral infection are related to immunocompetence of the host. Human immunodeficiency virus (HIV) infection increases the risk of HPV infection and the risk of developing HPV-related disease. All of the factors that predispose to persistent infection (those infections that do not clear) have not been elucidated. Persistent infections are associated with recurrent wart outbreaks and increase the risk of HPV-related malignancy.

Infectivity and Transmission

HPV is most commonly transmitted during sexual activity, which involves skin-to-skin contact; microabrasions in the area of contact permit the virus to be transmitted from one sexual partner to another. Even in the absence of visible lesions, such as a genital wart, the microabrasions expose the HPV-infected cells in the basal epithelium of the host and increase viral shedding. More importantly, microabrasions in the recipient expose vulnerable basal epithelial cells to the virus. About 60–66 % of sex partners of HPV-infected people will develop detectable HPV lesions, although they may be very subtle appearing or may be located in areas that escape normal detection [12]. About 50–55 % of men whose partners have cervical HPV disease have HPV-associated penile lesions [13]. HPV can also be transmitted from one woman to another [14].

Oral–genital contact can transmit infection. Early studies suggested that about 4 % of women with external genital warts also had buccal lesions. High-risk HPV has been found in about 25 % of oral cancers, supporting hypothesis there is some transmission via that route [15].

Perianal infection is quite common. Transmission is possible in men and women who have anal receptive sex with men. However, the presence of genital warts around the anus does not necessarily indicate a history of receptive anal intercourse. In one study, only 10 % of women who shed HPV from the anal area admitted to having anal intercourse, and 83 % of those with virus in the anal area, were also positive for HPV in cervical, vulvar, and vaginal samples [16].

The virus can also be transmitted by fomites. Transmission of the virus to the anogenital area has been reported in tanning beds and saunas. Other nondirect transmission may be possible via sex toys, exam tables, door knobs, and contamination of exam lights adjusted by examining hands [17].

Vertical transmission from mother to her newborn is possible, though rare, during delivery through an HPV-infected birth canal. The most serious complication that occurs for the newborn is respiratory/laryngeal papillomatosis. Genital warts and facial lesions in the infant can also result from exposure during delivery. However, it is not yet clear that cesarean delivery prevents HPV transmission to the baby and should only be performed if genital warts obstruct the birth canal.

Etiology

Papillomaviruses infect many animal species including cotton-tail rabbits, cattle, and humans. They are named and classified by their natural host. More than 120 different types of *human* papillomaviruses have been identified, but some have only been partially sequenced. HPV types are assigned new numbers when there is more than a 10 % difference in gene sequences in particular regions of the viral DNA and they

Table 1.1 Low risk vs. high risk HPV types

Low risk HPV types	High risk HPV types
Possess little to no oncogenic potential	Possess oncogenic potential
HPV 6,11,40,42,43,44,54,61,70,72,81 and CP6108	HPV 16,18,31,33,35,39,45,51,52,56,58,59, 68,73,82 and probably 26,53,66
Most commonly found on the external genitalia	Most commonly found as flat warts
Primarily responsible for external genital warts	Primarily responsible for intraepithelial neoplasias of the cervix, anus
Also responsible for juvenile respiratory papillomatosis	Also responsible for penile and anal carcinoma

Adapted from Munoz N, Bosch FX, de Sanjose S, et al. Epidemiologic classification of human papilloma-virus types associated with cervical cancer. N Engl J Med. 2003;348:518–27

are numbered in their order of discovery. All known HPV share a similar structure and genomic organization of small, non-enveloped virions with a double-stranded, circular DNA of 7800–7900 base pairs encased in an icosahedral protein capsid.

In general, genital HPV types have been classified into two groups based on the oncogenic potential—low- and intermediate/high-risk groups (*see* Table 1.1). The low-risk types (mainly 6 and 11) are responsible for almost half of the external genital warts. However, mixed viral types may be involved in the wart formation. The low-risk viral types have also been isolated from the lesions involved in laryngeal papillomatosis/respiratory papillomatosis in the tracheobronchial trees of children [18, 19]. The high-risk HPV types are primarily involved in the development of squamous cell cancerous lesions of the uterine cervix, anus, vulva, and penis [12, 20, 21], but also contribute to external genital warts. Four HPV types (6, 11, 16, and 18) account for 90 % of genital HPV infection.

Clinical Course

The usual reservoirs of genital HPV infection are the moist mucosa and adjacent squamous epithelia of the male and female genitalia, the cervix, and the anus. Microabrasions that develop during sexual activity enable the infected partner to shed virus and the uninfected partner to become more susceptible to infection. Repeated trauma in the area increases infectivity as wound healing stimulates cell division, increasing episomal viral replication [22]. The virus enters the basal epithelial cells in areas such as the inner labia minora in woman and the prepuce and frenulum in men. Anal epithelium is also traumatized easily during sex, permitting HPV infection. The virus also preferentially infects the rapidly dividing cells within the transitional zone of the cervix.

After introduction of the virus into the host basal epithelial cells, the virus sheds its protein capsule and coexists within the host cell as a circular episome. The virus then enters into a latent incubation period of 1–8 months, during which time there

are no visible manifestations of the infection. The active growth phase starts when the first lesion develops. It is not known what induces the transition from latent to infective stage, but many host, viral, and environmental factors are involved. During the active infection phase, the HPV replicates independent of host cell division and induces the host cells to proliferate, creating a myriad of lesions from flat to papillary warts. Viral counts are highest in the superficial layers of the epithelium, increasing infectivity. During this phase, patients generally seek therapy.

Approximately 3 months later, the host immune system mounts a response. The innate immune system is recruited and interferons slow HPV replication and trigger the cell-mediated immune response. An immunocompetent cell-mediated immune system and cytokine production are needed for HPV clearance, but there are still challenges to viral clearance in immunocompetent hosts. HPV has some protection from the host response because the virus is intracellularly located. In addition, the epithelial cells in the perineum do not present antigens well to the host, so the HPV may not be recognized by the immune system [23]. HPV blocks the host response by depleting local intraepithelial lymphocytes, Langerhan's cells, and CD4+ cells and down regulating cytokine production [22]. However, lysis of the infected cells exposes the HPV to the host and triggers more intense defense.

About 80–90 % of people will clear the infection so that the virus can no longer be detected. Only 10–20 % of individuals will have persistent infection that can express itself either as a latent infection, which may be periodically reactivated, or as a persistent (and more difficult-to-treat) infection. Recurrences are more likely when host immune system is compromised by chemotherapy, corticosteroid therapy, or HIV infection.

Clinical Manifestations

Genital warts can be found on the external genitalia, the vagina, cervix, anus, mouth, and larynx. Most patients with genital warts are asymptomatic. In a study of university women, neither acute nor persistent HPV infection (documented by viral shedding) was associated with discharge, itching, burning, soreness, or fissure [16]. Even women with genital warts had none of the associated symptoms. Patients with external genital warts may complain of a bump or mass they palpate or see on inspection. Infected or large lesions may be tender or associated with spotting, odor, or tenderness. Larger internal warts may produce dyspareunia or postcoital spotting. Urethral lesions may impair flow of urine or ejaculate. Condyloma acuminata are the classical external genital warts. They are raised, acuminate, exophytic lesions, which on keratinized skin are white, gray, or flesh-colored warty lesions. On mucosal surfaces, low-risk HPV tends to have finger-like projections and blend in color with surrounding tissue.

Another presentation of HPV in the genital area are papillomas. Papillomas are raised, possibly pigmented lesions, which are slow-growing and sometimes pedunculated. They are often mistaken for skin tags or moles and are most commonly found on keratinized skin.