

Strategies for Managing External Genital Warts

When to use topical therapy, when to choose surgery

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Human papillomavirus (HPV) infection may be the most common viral sexually transmitted disease (STD) in this country. As many as 30 million Americans are infected with HPV, and each year, an additional 1 million persons become infected. The economic burden is substantial. In 1994 alone, the costs associated with HPV infections (excluding HPV-related cancer) exceeded \$3.8 billion—more than one third of the approximately \$10 billion spent annually on STDs and related syndromes.^{1,2}

More than 80 distinct types of HPV have been identified; at least 20 of them can infect the genital tract. Infection due to HPV type 6 or 11 is usually associated with external genital warts, such as condylomata acuminata, whereas that due to HPV type 16 or 18 is associated with cervical, vulvar, and anal carcinomas.³

This article will focus on external genital warts—how HPV infection occurs, how the disease is transmitted, and which patients are most at risk. It also will explain how external genital warts can be differentiated from other lesions (including carcinomas), when a biopsy is required to confirm the diagnosis, and which

ABSTRACT: Infection with the human papillomavirus can lead to external genital warts as well as carcinomas of the cervix, vulva, and anus. The diagnosis is based on clinical examination, but when warts are pigmented, indurated, fixed, and ulcerated, biopsy is required. Condylomata acuminata are the classic lesions, but warts may also be smooth and dome-shaped (papular), thick and horny (keratotic), or flat-topped. The goal of treatment is to remove symptomatic lesions. Options include trichloroacetic acid or bichloroacetic acid (provider-administered) and imiquimod or podofilox (patient-applied). Resistant lesions that persist for longer than 3 months may respond to cryotherapy and interferon. (*Women Health Primary Care* 1998;1(4):320-326)

treatment approach is best for your patient.

PATHOGENESIS

The natural course of HPV infection involves 5 distinct phases:

- ◆ Inoculation.
- ◆ Incubation.
- ◆ Active expression.
- ◆ Host containment.
- ◆ Latency.

HPV infection likely begins with an abrasion of the epithelial surface. The wound provides viral access to the basal layer of the squamous epithelium. During wound healing, basal and parabasal cell division accelerates, and the blood supply at the abrasion site is stimulated. This process may actually facilitate viral replication.

After inoculation, an incubation period begins and lasts from 4 weeks to 8 months. The incubation period is followed by an active expression phase. This phase is marked by rapid epithelial capillary proliferation that usually persists from 3 to 6 months. It is during this phase that clinically obvious lesions emerge (Figure 1) or subclinical lesions develop.

Although intraepithelial macrophage-like cells initiate a cell-mediated immune response, humoral immunity appears to be delayed, most likely because of the intraepithelial location of the virus. However, approximately 3 months after the initial proliferative phase and the appearance of the clinical manifestations of the disease, a humoral immune response can be detected. The result is a suppression of new

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lesions. This is known as the host containment phase. It is clear that an intact immune system is at least as important as any of the available therapies for HPV infection in resolving the clinical manifestations of this disease.

After about 9 months, a latent phase begins. This phase is characterized either by sustained clinical remission or by a continued active disease expression; the latter may place the patient at risk for neoplastic progression.⁴⁻⁷ In some patients, particularly younger women, the infection may resolve.

The histologic findings during the early and late phases of HPV infection are described in Table 1. Additional information about the biology of HPV infections can be found on page 325.

TRANSMISSION

Genital HPV infection is transmitted by intimate sexual contact.⁸ Early age at first coitus, multiple sex partners, and coitus with a person who has external genital warts are risk factors for HPV infection (Table 2).⁹ (Infectivity may be greater for persons with clinically apparent external genital warts than for those with subclinical infection.) The use of oral contraceptives and smoking also appear to increase the risk. Although intra-anal warts are associated with anoreceptive intercourse, perianal warts are not.¹⁰

The elapsed time from HPV transmission to the clinical appearance of lesions is highly variable; it may be as brief as 4 to 6 weeks⁷ or as long as 8 months.⁸ The most common site of the warts is the posterior introitus, an area where minor abrasions and tears would be expected



Figure 1. The condyloma warts depicted here appeared during the active expression phase of human papillomavirus infection.

during intercourse. However, the infection may remain asymptomatic. In one study involving women with documented cervical condylomata, most of their male partners had evidence of the disease on biopsy, but only 16% of these men had visible lesions (72% had subclinical infection).¹¹

Vertical transmission—from mother to infant—of HPV is uncommon; only 1,500 new cases of juvenile laryngeal papilloma (which has been associated with perinatal HPV transmission) occur each year.¹² One would expect a

lifetime risk for all children (not just those born to mothers with HPV infection) to approximate 1:2,000. However, the Collaborative Perinatal Study failed to identify a single case of perinatal HPV transmission among 44,000 children, even though the rate of HPV detection (by polymerase chain reaction) increased from 51% to 59% during the mothers' pregnancies.¹³ Delivery by cesarean section, if not indicated for obstetrical reasons, is not recommended for infected women unless external genital warts are obstructing the birth canal.

DIAGNOSIS

Clinical examination has been proved (in trials involving immunocompetent patients) a reliable method of establishing a diagnosis of external genital warts; its findings are consistent with the histologic changes associated with HPV infection. Because HPV can cause warts to form in the vagina, on the uterine cervix, and inside the urethra and anus, as well as on external structures, careful evaluation of the entire genital region is required.

A magnifying glass and a bright light may be helpful, particularly for identifying flat or small lesions. Although the acetowhite test (acetic acid solutions of 3% to 5% applied to genital tissues for 5 to 10 minutes) has been used for diagnosis, it cannot be recommended

because of its low specificity.

Cervical cytology, despite its low sensitivity, often can pick up the characteristic koilocyte; it is the most common method of detecting subclinical disease. Vulvar biopsy should be performed whenever the diagnosis is in question and particularly when the

Table 1. Histologic signs of HPV infection

Early stage

Hyperplastic proliferation of basal cells and parabasal cells (acanthosis)
 Degenerative cytoplasmic vacuolization (koilocytosis)
 Thickening of the superficial cell layers (hyperkeratosis, parakeratosis)
 Nuclear wrinkling, pyknosis, and binucleation

Late stage

Episomal basal cell infection
 Replication only once per cell cycle
 Subclinical in most cases

HPV, human papillomavirus.

lesions do not respond to standard treatment; the disease worsens during therapy; the patient is immunocompromised; or the warts are pigmented, indurated, fixed, and ulcerated.

There are four morphotypes of external genital warts:

- ◆ Classic condylomata acuminata have the appearance of small cauliflowers (Figure 2).
- ◆ Papular warts are smooth, dome-shaped, and usually flesh-colored, and they characteristically appear as papules, 1 to 4 mm in diameter.
- ◆ Keratotic genital warts have a thick, horny layer and may resemble a common wart or a seborrheic keratosis.
- ◆ Flat-topped papules may be flat or slightly raised.

The wart morphotype may be influenced by the type of skin infected. Acuminate warts tend to occur on moist surfaces (such as the vulva, introitus, and perianal area), whereas keratotic warts and smooth papular warts form on fully keratinized skin (lateral labia majora). Flat warts may appear on either surface.

External genital warts should not be confused with normal structures, such as vestibular papillae and sebaceous glands. In addition, these warts can be difficult to distinguish from molluscum contagiosum, seborrheic keratosis, lichen planus, skin tags, melanocytic nevi, pseudoverrucous papules, and condyloma latum. The flat, sometimes erythematous genital lesions found in patients with psoriasis, seborrheic dermatitis, or squamous cell carcinoma also should not be mistaken for external genital warts.

Bowenoid papulosis is almost always associated with infection due to

Table 2. Risk factors for genital HPV infection

Early age at first coitus
Coitus with a partner who has external genital warts
Multiple coital partners
Oral contraceptive use
Smoking
HPV, human papillomavirus.

HPV type 16 or 18; it usually presents as pigmented, dome-shaped, or flat papules that can be difficult to distinguish from external genital warts. Pigmented lesions of the vulva require biopsy. Histologic findings often reveal high-grade squamous dysplasia. The Buschke-Löwenstein tumor, a form of verrucous squamous cell carcinoma, is the only neoplastic lesion associated with the low-risk HPV types 6 and 11.

Women with HPV infection—and their sexual partners—should be examined for other STDs. Tests for syphilis, gonorrhea, and chlamydial or HIV infection should be considered. Routine screening for cervical cancer should be performed annually; more frequent Pap tests are not required by a diagnosis of external genital warts.

TREATMENT

The primary goal of treatment is to remove symptomatic warts.¹⁴ It is

important to remember, however, that HPV infection can be a chronic disease. Although proper treatment may induce lesion-free periods, no evidence exists that any available therapy can eliminate the in-

fection.¹⁵ Recurrences may be caused by patient-specific biologic factors related to local immunity.

External genital warts may resolve without treatment. As many as 21% of vulvar lesions regress over 16 to 20 weeks, but up to 79% persist—prompting most women to seek treatment. Although observation is an alternative to standard therapy, intervention is needed to promote the resolution of most lesions. Involve the patient as an active partner in the development of a treatment plan. No single therapy is ideal for all women or all warts; most are similar in efficacy. Smoking cessation also can be helpful.

The available therapies for external genital warts are either patient-applied or provider-administered. Our management approach is summarized in Figure 3. Because most patients have 1 to 10 warts, with a total wart area of 0.5 to 1.0 cm², we begin with a provider-administered therapy, usually bichloroacetic acid (BCA); trichloroacetic acid (TCA) is an alternative. Apply BCA or TCA only to the visible warts; avoid surrounding areas of skin that appear normal.

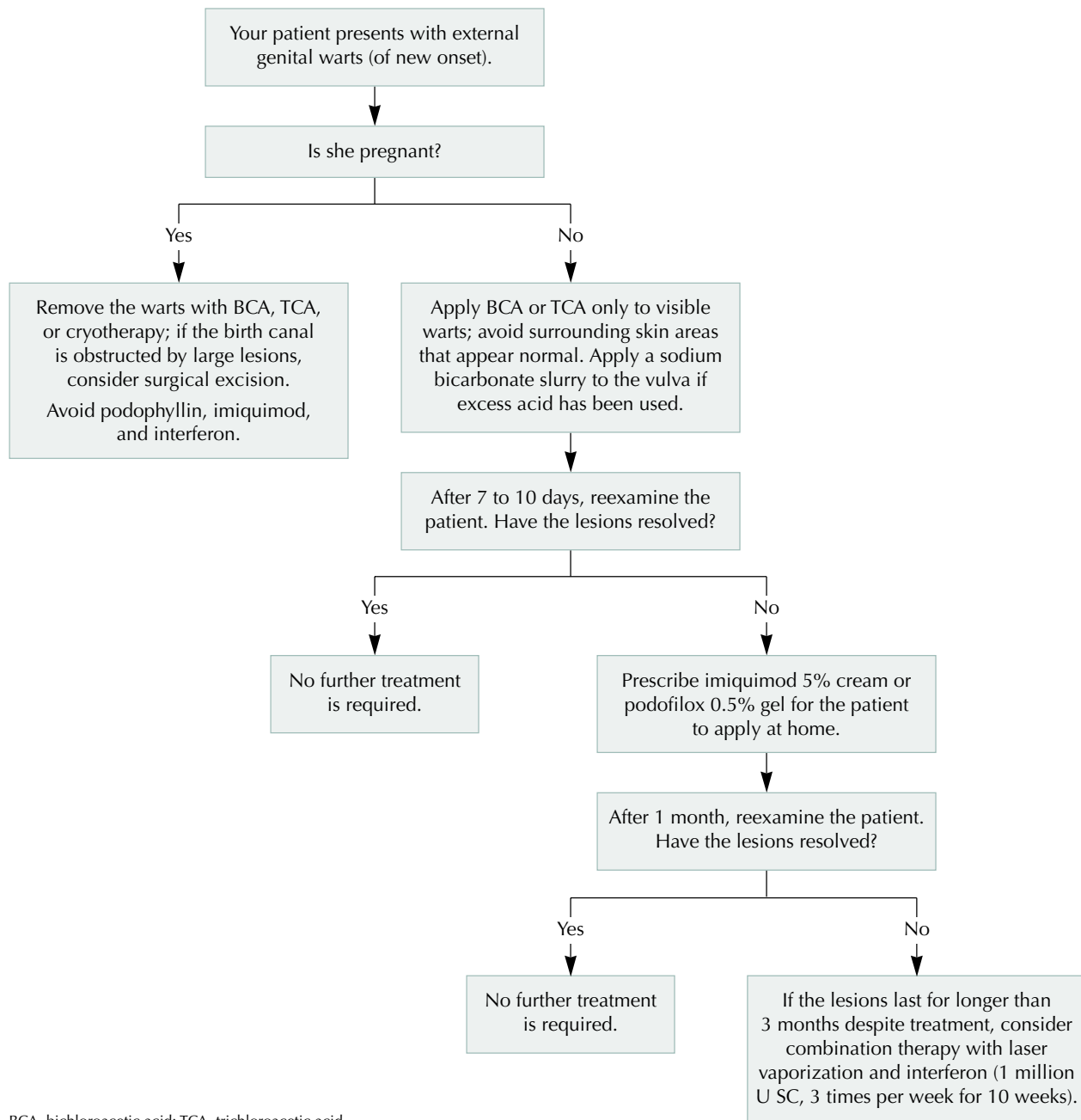
If excess amounts of acid have been used, apply a sodium bicarbonate slurry to the vulva. Ask the patient to return for a follow-up visit in 7 to 10 days.

If disease resolution is noted during the sec-



Figure 2. Vulvar condyloma are easily visible following application of a 3% acetic acid solution.

Figure 3. A management algorithm for external genital warts



BCA, bichloroacetic acid; TCA, trichloroacetic acid.

ond visit, no further therapy is required. However, if new lesions are evident, the patient should be presumed to be in the proliferative phase of HPV infection. Prescribe a patient-applied treatment, either imiquimod 5% cream or podofilox 0.5% gel.

Imiquimod is a topically active immune enhancer; it eliminates external genital warts by stimulating the production of interferon and other cytokines.¹⁶ Instruct your patient to apply imiquimod 3 times weekly and, 6 to 10 hours after each application, to wash the treat-

ment area with mild soap and water. She should continue imiquimod therapy until her lesions resolve, up to a total of 16 weeks. Most warts will clear within 8 to 10 weeks, or sooner. Warn your patient to expect a mild-to-moderate inflammatory reaction to the drug

before her warts disappear.

Podofilox gel is an antimitotic agent. Instruct your patient to apply the medication to her visible warts twice daily for 3 days and then to withhold treatment for the next 4 days. This cycle can be repeated as needed, up to 4 times. Caution your patient to anticipate mild-to-moderate pain or local irritation before her warts are destroyed by podofilox.

Remember that the patient must be able to identify and reach her warts for these self-applied therapies to be successful. Ask her to return for a visit in 1 month.

If the warts are resistant to standard treatment (that is, the lesions last for longer than 3 months), consider combination therapy with laser vaporization plus interferon (1 million U administered subcutaneously 3 times per week for 10 weeks).¹⁷ Imiquimod may be an alternative to interferon in this setting, but confirmatory studies are required.

During pregnancy, external genital warts can proliferate and become more friable; thus, we advocate their removal. Avoid using podophyllin resin, imiquimod, and interferon in pregnant women. Instead, initiate therapy with BCA or TCA, or consider the judicious use of cryotherapy. If large lesions appear to be obstructing the birth canal, surgical excision may obviate the need for delivery by cesarean section.

A follow-up evaluation after visible genital warts have cleared is not mandatory. Patients should be advised to watch for recurrences, which develop most frequently during the first 3 months. However, follow-up visits may be useful for documenting a wart-free state, monitoring treatment compliance and complications, and providing patient education and counseling. The presence of external genital warts is not an indication for colposcopy of the cervix or for more

The biology of human papillomavirus infection

The human papillomavirus (HPV) is a nonenveloped icosahedral, double-stranded DNA virus with an outer shell composed of two polypeptides. Its genome is about 8,000 base pairs in size. More than 80 distinct types of HPV have been identified (types are differentiated based on DNA homology and/or sequence).

HPV infects the basal layer of the squamous epithelium. Early gene products are detectable near the epithelial basement membrane; late gene products (the viral capsid and completed virion) are only detectable in the terminally differentiated epithelial cells. Hyperplasia of the basal and parabasal epithelial cells, coupled with a progressive thickening of the squamous epithelium and koilocytotic changes (the pathognomonic cytopathological effect of HPV), give rise to the characteristic histologic appearance (Figure 4).

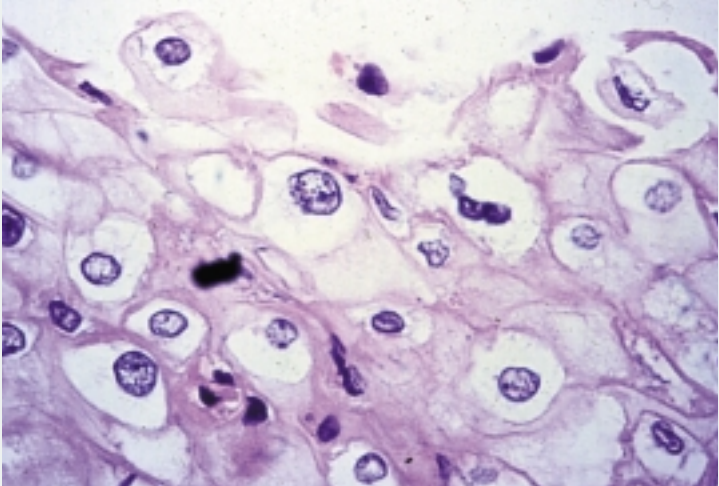


Figure 4. Koilocytic atypia characterizes the histologic appearance of tissue infected with human papillomavirus. Note the central clearing of the cytoplasm and the binucleation.

frequent Papanicolaou smears.

Examination of the sex partners of HPV-infected women is not necessary for the management of their external genital warts because the role of reinfection in persistent disease is probably minimal. However, such examination is recommended to detect other STDs or previously unrecognized visible warts. Use of condoms can reduce but not eliminate transmission of HPV to uninfected partners. Patients should

understand that they may remain infectious even after their visible warts have resolved. ❁

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PRIMARY POINTS

External Genital Warts

Infection with the human papillomavirus (HPV) may be the most common sexually transmitted disease of viral origin in this country. HPV types 6 and 11 are associated with external genital warts, whereas HPV types 16 and 18 can cause cervical, vulvar, and anal carcinomas.

Risk factors for HPV infection include early age at first coitus, multiple sex partners, and coitus with a person who has external genital warts; the use of oral contraceptives and smoking also may increase the risk.

The diagnosis of external genital warts is based on clinical examination. Classic condylomata acuminata have the appearance of small cauliflowers; however, the warts may be smooth, dome-shaped, and flesh-colored (papular), may have a thick, horny layer (keratotic), or may be flat or slightly raised (flat-topped).

Biopsy is needed whenever the diagnosis is in question and particularly when the lesions do not respond to standard treatment; the disease worsens during therapy; the patient is immunocompromised; or the warts are pigmented, indurated, fixed, and ulcerated.

Although some external genital warts may resolve without treatment, most require therapy. No single treatment is superior to another. Options include bichloroacetic acid (BCA), trichloroacetic acid (TCA), imiquimod 5% cream, and podofilox 0.5% gel. Resistant lesions may respond to combination therapy with laser vaporization and interferon.

If the patient is pregnant, external warts should be removed with BCA, TCA, or cryotherapy; podophyllin resin, imiquimod, and interferon should be avoided. If large lesions are obstructing the birth canal, surgical excision should be considered.