

Condylomata acuminata (anogenital warts)

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INTRODUCTION — Anogenital warts (condylomata acuminata) is the most common viral sexually transmitted disease in the United States. Although condylomata affect both genders, data from office visits for warts obtained from the 1994 to 1998 National Ambulatory Medical Care Survey showed that women accounted for 67 percent of the patient population [1].

ETIOLOGY — Condyloma acuminatum is caused by human papilloma virus (HPV) infection. HPV encompasses a family of highly infectious and primarily sexually transmitted double-stranded DNA viruses. The incubation period after exposure ranges from three weeks to eight months. Most infections are transient and cleared within two years [2]. Persistent infections in the setting of other clinical risk factors (such as infection with the human immunodeficiency virus) is associated with the development of squamous cell carcinoma [3,4]. There are over 70 distinct HPV subtypes; approximately 35 types are specific for the anogenital epithelium and have varying potentials to cause malignant change, such as cervical or anal cancer ([show table 1](#)) [5]. HPV serotypes 16 and 18 are most commonly associated with squamous cell carcinoma. Low-risk subtypes, such as HPV 6 and 11, do not integrate into the host genome and are most frequently associated with benign condylomas and low grade intraepithelial neoplasia ([show table 2](#)). Intermediate risk subtypes can cause high grade dysplasia which persists but rarely progresses to the invasive stage.

RISK FACTORS — Acquisition of condylomata is related to sexual activity. Digital/anal, oral/anal and digital/vaginal contact probably can also spread the virus, as may fomites [6]. The disease is also more common in immunosuppressed individuals [7,8].

Women — Disease in women is primarily caused by vaginal intercourse. Anal condylomata can occur by extension from vulvar or perineal infection or by receptive anal intercourse. The risk of disease increases with the number of sexual partners. A population-based case-control study including 94 women with incident and 55 women with recurrent condyloma found women with five or more partners within the previous five years were over seven times more likely to have incident condyloma and over 12 times more likely to have recurrent condyloma compared to women with only one sexual partner during the same time period [9]. An increased risk of incident condyloma was also associated with a history of any sexually transmitted disease or oral herpes.

Men — In men, the preputial cavity or penile shaft can be affected through heterosexual or homosexual activity. Perianal lesions may occur among heterosexual men, although most such lesions are observed

among men who have sex with men. The risk of disease increases with the number of sexual partners [10], as described above for women.

HIV infected individuals — The prevalence of condyloma is higher in patients who are HIV positive or who have other forms of sexually transmitted diseases [11-14]. In an illustrative study, the prevalence of condylomata acuminata in 385 HIV-1 positive and 341 HIV-1 negative women was 7 and 1 percent, respectively [14]. Lower CD4 T lymphocyte count (<500 cells/ μ L) and frequent injection of drugs were also risk factors for development of vulvovaginal or perianal lesions. Similar results were reported in a subsequent study, which also noted that highly active antiretroviral therapy were associated with lower rates of these lesions [15].

CLINICAL MANIFESTATIONS — Symptoms associated with condylomata acuminata vary depending upon the number of lesions and their location. Patients with a small number of warts are often asymptomatic. Other patients may have pruritus, bleeding, burning, tenderness, vaginal discharge (women), or pain.

Condylomata can occasionally form large exophytic masses that can interfere with defecation, intercourse, or vaginal delivery. Lesions involving the proximal anal canal may also cause stricturing.

DIAGNOSIS — The diagnosis of condylomata can usually be made by visual inspection of the affected area. The lesions, which are skin-colored or pink, range from smooth flattened papules to a verrucous, papilliform appearance ([show picture 1](#)). (See "[Clinical presentation and diagnosis of human papillomavirus infections](#)", sections on Clinical manifestations and diagnosis).

The extent of involvement should be documented by anoscopy, sigmoidoscopy, colposcopy, and/or vulvovaginal examination, as appropriate. High-resolution anoscopy is being used increasingly to permit improved visualization of the tissue [16]. In addition, application of 5 percent [acetic acid](#) causes lesions to turn white, which facilitates identification but is not specific. A biopsy can be considered when the diagnosis is uncertain, in those who do not respond to therapy, in immunocompromised patients, in those with large lesions, or in the presence of atypical features ([show table 3](#)). Some authorities recommend a routine biopsy to search for dysplasia [17].

Differential diagnosis — Condyloma acuminatum ([show picture 1](#)) should be distinguished from another form of condylomata (condyloma lata), which is caused by secondary syphilis infection. Lesions in condyloma lata appear flat and velvety ([show picture 2](#)).

Micropapillomatosis of the vulva is a normal variant. The papillary projections each arise from an individual base, in contrast to condyloma acuminatum where multiple papillae arise from a single base. Painful verrucous perianal lesions have been described in association with herpes simplex in patients with AIDS [18].

Squamous cell carcinoma of the anogenital area can exist concurrently with condylomata acuminata. Suspicious lesions (particularly those which are ulcerated) should be biopsied. Lesions that do not respond after three provider administered treatments or have not resolved after six months should be reevaluated with consideration of biopsy to confirm the diagnosis [19]. Patients who are immunocompromised, or over 40 years of age, or have large, pigmented, or atypical lesions also warrant a higher index of suspicion of malignancy.

Additional conditions which should be considered include hymenal remnants and vulvar intraepithelial neoplasia (in women), molluscum contagiosum (see "[Molluscum contagiosum](#)"), skin tags, and angiofibromas ([show picture 3](#)).

TREATMENT — Treatment of condyloma acuminatum involves one of three major approaches: chemical or physical destruction, immunologic therapy, or surgical excision ([show algorithm](#)). Limited experience with topical antimicrobial therapy has also been reported. The preferred approach depends upon the number and extent of the lesions. In general, all therapies for genital warts are somewhat unsatisfactory due to recurrence rates of 30 to 70 percent within six months of treatment [20]. However, spontaneous regression is also possible, and has been reported to occur within three months in 20 to 30 percent of cases.

There is no evidence to suggest that one treatment is significantly superior to another or appropriate for all patients and all types of warts [19]. If a clinician has [trichloroacetic acid](#) or podophyllin available in their office practice, then it would be most efficient for the clinician to provide an initial treatment of the warts at the diagnostic visit, and then to prescribe home treatments ([imiquimod](#) or [podofilox](#)) or examine the patient in follow-up to see how the initial treatment worked. For clinicians without trichloroacetic acid or podophyllin in their office, the patient could first try home treatments (imiquimod or podofilox). However, we suggest initially referring patients with very large condylomata to a surgeon (gynecologist or anorectal surgeon) because surgical treatment is probably going to be needed.

Chemical agents — Chemical agents include podophyllin, [trichloroacetic acid](#), and 5-fluorouracil/[epinephrine](#) gel ([show table 4](#)).

Podophyllin — Podophyllin, an extract of [Podophyllum](#) peltatum, contains the antimitotic agent podophyllotoxin, which arrests the cell cycle in metaphase and leads to cell death. Podophyllin solution when used topically as a single agent once or twice a week has limited success in clearing warts (from 20 to 50 percent clearance at three months) [21]. It is usually used as a 25 percent solution in combination with another treatment method such as cryotherapy. The solution is applied to a small area of skin, allowed to dry, and then washed off within six hours of application. Large areas should not be treated in a single application because of potential neurotoxicity and pain when the area becomes necrotic. Podophyllin should never be applied to the cervix or vaginal epithelium because of risk of chemical burns.

The drug is teratogenic and must not be used in pregnancy or suspected pregnancy. It is not indicated for internal (eg, mucosal) use. Adverse effects range from mild skin irritation to ulceration and pain depending upon the concentration used and the length of time over which it is applied to the skin.

A similar agent, 0.5 percent [podofilox](#) (podophyllotoxin) can be self-administered. It is applied to palpable external warts twice daily for three days, followed by a four day rest period, then repeated up to four times. The surface area treated and the volume of medication per application should not exceed 10 cm² and 0.5 mL, respectively. A randomized trial comparing self-administration of podophyllotoxin solution or cream (0.5 and 0.15 percent, respectively) to 25 percent podophyllin administered in a clinic found that self treatment of anogenital warts with podophyllotoxin showed greater efficacy and cost-effectiveness than clinic based treatment with podophyllin [22]. However, recurrence of warts within 12 weeks of study entry occurred in 43 percent of all initially cleared subjects, without significant differences among the treatment groups.

Trichloroacetic acid — [Trichloroacetic acid](#) (80 to 90 percent concentration) physically destroys the wart tissue by protein coagulation. Clearance rates and adverse effects are similar to podophyllin. Repeated application is required. However, in contrast to podophyllin, trichloroacetic acid can be used for internal lesions [23] and during pregnancy, when it is considered first line therapy. The solution is highly caustic and should not be applied to skin surrounding the lesion; a barrier of petroleum jelly helps to protect unaffected areas nearby.

5-fluorouracil epinephrine gel — [Fluorouracil](#) is a pyrimidine antimetabolite that interferes with DNA synthesis by blocking the methylation of deoxyuridylic acid, leading to cell death. A gel consisting of 5-fluorouracil and [epinephrine](#) can be injected intralesionally. One study evaluated the safety and efficacy of this treatment in 401 patients randomly assigned to receive fluorouracil/epinephrine gel, fluorouracil gel alone, or placebo [24]. Each lesion was injected once per week for up to six weeks, and patients were followed for three months. The complete response rate was higher in patients treated with fluorouracil/epinephrine gel than fluorouracil gel without epinephrine or placebo, 61 versus 43 and 5 percent, respectively. However, the recurrence rate in patients with complete response to drug therapy was 50 to 60 percent at three months.

Immune modulation — [Imiquimod](#) and interferon alfa are the two immune modulating agents that have been used ([show table 4](#)).

Imiquimod — [Imiquimod](#) is a positive immune response modifier, which acts by local cytokine induction. It is applied topically as a 5 percent cream and has shown significant effect in clearing warts (72 to 84 percent of patients) with few recurrences (5 to 19 percent) in limited clinical experience [23,25,26]. Most patients who do not clear still have a significant reduction in lesion size. Imiquimod has also been used for treatment of vulvar and anal intraepithelial neoplasia [27,28]

[Imiquimod](#) is not indicated for internal use. The cream is applied and left in place for six to ten hours, and then washed off. Treatment can be performed at home, three times per week for up to 16 weeks. The major side effect is mild to moderate local erythema.

Interferon alfa — Primary systemic therapy with interferon can achieve complete resolution of the anal condyloma in 25 to 80 percent of patients, but is frequently associated with interferon-related side effects and recurrence [29,30]. Interferon may also be given intralesionally [31]. Interferon is not FDA approved for treatment of anogenital warts, but is widely used for this purpose.

- In one study, 203 patients with untreated anogenital condyloma were randomly assigned to one of four treatment groups with varying doses of interferon (3 million units IM daily for three weeks or 3 million units SQ three times per week for four weeks), diathermocoagulation, or no treatment [30]. After six months, the overall complete response rate was similar for patients receiving interferon compared to diathermocoagulation (57 versus 82 percent respectively, compared to 8 percent for untreated patients). However, the disease recurred significantly more often in patients who were treated with interferon (15 versus 4 percent).

Local or systemic treatment with interferon may also decrease the likelihood of recurrence following surgical excision or ablative therapy, but is uncommonly used in clinical practice [4,32].

- In one study, 81 patients with condylomata acuminata who had undergone treatment with either 5-fluorouracil cream or laser ablation were randomized to adjuvant alpha-interferon therapy or no additional treatment [4]. At the end of eight weeks, recurrences were less common in patients who had received interferon (6 versus 24 percent).

Surgery — Ablative or excisional surgical therapy may be considered when medical therapy has failed or when warts are amenable to surgical removal. Cryotherapy can be performed in an appropriately equipped office, but laser and excisional therapy require an operating room and thus are usually a last resort after other methods have failed. However, very large lesions may be considered for excisional surgery as an initial approach.

Cryotherapy — Cryotherapy can be performed in the office by the application of liquid nitrogen spray, a swab soaked in liquid nitrogen, or by placing a [nitrous oxide](#) cooled cryoprobe on the lesion. This procedure is safe in pregnancy. This method causes pain during application and variable localized inflammation afterward. Clearance rates at three months are 63 to 92 percent [23], and again repeated application is required.

The ice ball should extend 2 to 3 mm beyond an external lesion and 5 mm beyond cervical warts. [Nitrous oxide](#) should not be used in the vagina, but is preferred to liquid nitrogen for cervical warts because it produces better freezing of cervical tissue.

Laser therapy — Laser therapy (CO2 or NdYag) is carried out in the operating room or ambulatory surgical facility and requires anesthesia. A colposcope is useful for directing laser therapy in women. The tissue absorbs the laser energy, which is converted to heat energy, vaporizing the wart. Tissue destruction should not go beyond 1 mm in depth.

This technique has rates of wart clearance which approach 100 percent over one year [33]; however, recurrence can be up to 45 percent [23]. Adverse events include scarring and pain. The laser operator is also at risk for developing mucosal warts. This is the most expensive method of treating warts [34].

Excisional procedures — Knife or scissor excision requires anesthesia and involves routine surgical risks such as infection and hemorrhage. The three-month clearance rates are 36 percent [23]. The area of the lesion is excised down to normal skin or mucosa, and the roots of the lesions are cauterized. Care should be taken to assure that cauterization does not extend into the subcutaneous or submucosal fat. Excessive cauterization increases the risk of dysfunction from development of a stricture. Excised condylomata should be examined pathologically to exclude the presence of squamous cell carcinoma.

In pregnant women, large lesions can obstruct the vagina and may be lacerated during vaginal delivery. Such lesions should be treated aggressively or the patient delivered by cesarean section.

Topical antimicrobials — A newer approach beginning to appear in the literature involves topical application of antimicrobials, including [cidofovir](#) and bacillus Calmette-Guerin (BCG). Both therapies require further study.

Cidofovir — After undergoing cellular phosphorylation, [cidofovir](#) competitively inhibits the incorporation of dCTP into viral DNA by viral DNA polymerase. Incorporation of the drug disrupts further chain elongation.

A double-blind, randomized trial compared topical [cidofovir](#) gel containing 1 percent drug to a placebo gel in 30 patients with condylomata acuminata [35]. Patients were treated once daily for five days every other week for a maximum of six cycles with follow-up of six months for complete responders. Patients receiving cidofovir were more likely than placebo recipients to have a complete (47 versus 0 percent) or partial (37 versus 18 percent) response; five patients in the placebo group had progression of lesions compared to zero receiving cidofovir. One complete responder had a recurrence of lesions in the same location 120 days after finishing treatment. Four patients discontinued cidofovir applications.

Bacillus Calmette-Guerin — Ten patients were treated with topical BCG in one series with response in six at a mean of nine months follow-up, partial response in one, and no response in three [36].

Infrared coagulation — Infrared coagulation achieves tissue coagulation by focusing a narrow beam of infrared light delivered through a probe. The technique (Redfield Corporation, Rochelle Park, NJ) is approved for treatment of hemorrhoids, removal of tattoos, treatment of chronic rhinitis, ablation of common warts and anogenital condyloma. In one of the largest studies, successful treatment was described 61 of 74 (82 percent) women with condylomata acuminata of the genital tract [37].

INFORMATION FOR PATIENTS — Educational materials on this topic are available for patients. ([See "Patient information: Human papillomavirus \(HPV\) vaccine"](#) and [see "Patient information: Condyloma \(genital warts\) in women"](#)). We encourage you to print or e-mail these topic reviews, or to refer patients to our public web site, www.uptodate.com/patients, which includes these and other topics.

SUMMARY AND RECOMMENDATIONS

- Anogenital warts (condylomata acuminata) is the most common viral sexually transmitted disease in the United States.
- It is caused by human papilloma virus (HPV) infection. HPV encompasses a family of highly infectious and primarily sexually transmitted double-stranded DNA viruses.
- Acquisition of condylomata is related to sexual activity. Digital/anal, oral/anal and digital/vaginal contact probably can also spread the virus, as may fomites . The disease is also more common in immunosuppressed individuals.
- Symptoms vary depending upon the number of lesions and their location. ([See "Clinical presentation and diagnosis of human papillomavirus infections"](#)). Patients with a small number of warts are often asymptomatic. Other patients may have pruritus, bleeding, burning, tenderness, vaginal discharge (women), or pain.
- The diagnosis of condylomata can usually be made by visual inspection of the affected area. The lesions, which are skin-colored or pink, range from smooth flattened papules to a verrucous, papilliform appearance ([show picture 1](#)).
- Treatment involves one of three major approaches: chemical or physical destruction, immunologic therapy, or surgical excision. We agree with the approach summarized in the algorithm ([show algorithm](#)). The preferred approach depends upon the number and extent of the lesions.
- In patients with recurrence following successful initial treatment, we suggest either excisional or fulguration therapy ([Grade 2C](#)). An acceptable alternative is cryotherapy but we prefer the combination of excision/fulguration since it allows us to obtain a biopsy of at least part of the specimen. After the area heals, we generally use "adjuvant" treatment. We typically start this therapy four weeks after excision and most commonly use [Imiquimod](#) 5 percent cream (Aldara) applied three times per week for 12 weeks.