An Updated Overview for Management of Genital Warts

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Abstract

Background: Genital warts (condylomata acuminata) (GWs) are benign epithelial mucosal tumors caused by human papillomavirus (HPV); most frequently types 6 and 11. Genital warts usually appear as a few small, raised lesions. They may be small or may enlarge and combine into masses. They can be many or only one. They may be flesh-colored, gray, dark purple or brown. They can be rounded bumps or flat plaques, smooth or rough. They may be hidden in hair or folds of skin. They are mostly painless but may itch or become irritated. GWs treatment includes topical chemicals or drugs, excisional surgery, electrosurgery, cryosurgery, laser surgery, and intralesional immunotherapy. There is no evidence that one treatment option is superior to another, and no single treatment is perfect for all patients or all warts. Several factors affect the choice of treatment for a single patient as: wart size, number, anatomic site, cost, patient preference, side effects, and doctor’s experience. The available treatments, unfortunately, might be painful and leave a scar or hypopigmentation; moreover, recurrence rates after any treatment range from 6% to 100%.

Keywords: Genital warts

Background

Genital warts (condylomata acuminata) (GWs) are benign epithelial mucosal tumors caused by human papillomavirus (HPV); most frequently types 6 and 11. Genital warts usually appear as a few small, raised lesions. They may be small or may enlarge and combine into masses. They can be many or only one. They may be flesh-colored, gray, dark purple or brown (1).

In women, genital warts may be found on the vulva, in the vagina, and on the cervix. In men, they arise mostly in areas exposed to trauma during coitus such as the scrotum, in and around the tip of the penis, and on the shaft of the penis. Warts can be found in the groin or in or around the anus in both men and women (1).

Management of Genital Warts

Subclinical lesions: treatment is not recommended. (2)

AGWs:

♦ The main aim of treatment is to eliminate visible warts.
♦ Removal of warts through any therapy does not mean the eradication of human papillomavirus (HPV) infection.
♦ No gold standard treatment.
♦ With any treatment, recurrence is common.
♦ Topical treatment of AGWs placed in moist, occluded areas may be more effective than treatment of partly keratinized areas such as the penile shaft. Beutner, et al (3)
Treatments may be patient- (self) or clinician-applied. The choice of treatment should be guided by:

- Clinician's experience,
- Patient preference,
- Size, shape, number, and site of lesions,
- Availability of resources,
- Cost and Potential adverse effects. (2)

**Considerations for other sexually transmitted infections**

During medical visits for anogenital warts, screening for other STIs helps doctors identify common yet asymptomatic co-infecting diseases and supports efforts to improve patient treatment. (4)

**Considerations in pregnant and breastfeeding women**

In pregnancy and breastfeeding, warts may enlarge and multiply. Except for trichloroacetic acid (TCA), topical treatments should be avoided. Ablation using cryotherapy or any surgical treatment modality is acceptable. Laser therapy has been proven effective and safe. The presence of warts rarely impacts the mode of delivery unless there is obstruction of the birth canal due to very large warts. (5)

**Considerations in children**

Condylomata acuminata in children may be, but are not necessarily, an indicator of sexual abuse. In the case of condylomata in childhood, there should be a pediatric gynecological examination concerning abuse-associated findings and screening for concomitant sexual diseases, history should be taken concerning maternal or familial condylomata and any abnormalities showed by the child. (5).

**Considerations in those who are immunocompromised**

In HIV-positive patients, a recent systematic review and meta-analysis of treatments found evidence to support imiquimod for the partial clearance of external warts only. Prolonged or repeated treatments may be necessary. (6)

**Partner notification**

Partner notification (or contact tracing) is the process by which the sexual contacts of a patient with an STI are informed that they may be at risk. They are then offered to screen, and treatment if needed. The goal is to find and treat undiagnosed, often asymptomatic, infections. This helps to decrease re-infection in the index patient, and the spread of STIs in the community. (7)

**Treatment:**

Until a few years ago, the only treatment of genital warts consisted of combined or sequential treatment with cryotherapy, podophyllotoxin, and laser ablation. Since then, new pharmacological agents and methods have broadened the spectrum of therapeutic options. The present review attempts to offer an overview of all treatments for condylomata acuminata currently available and to translate the significance, usefulness of different treatment options (8).

Available current treatment options of CA are largely centered upon removal of the warty tissue rather than elimination of the underlying viral infection. There is little evidence to suggest that current treatments are effective in the long-term eradication of genital warts or that they play any significant role in hindering potential malignant wart development. Presently, a wide range of therapies is in use, which is highly variable and can differ dramatically concerning cost, side-effect profiles, dosing schedules, duration of treatment, and overall effectiveness (8).

As of yet, no definitive therapy has appeared as the ideal standard of care in the treatment of condylomata acuminata, and therapy selection generally occurs in a patient-specific manner (8). The common treatments can be divided generally into two categories: provider-administered treatment and self-administered treatment. The provider-administered treatments chiefly include ablative therapy...
(e.g. cryoablation, laser ablation, microwave ablation, and electrosurgery) and non-ablative therapy (e.g. trichloroacetic acid). The self-administered treatments mainly include podophyllotoxin, imiquimod, and polyphenon E (9).

The common treatment modalities being used for warts cause pain, scarring and are associated with high recurrence rates. Immunotherapy is an emerging treatment option that is non-destructive, easy to administer, and associated with lesser side effects (9).

Table (1): Treatment modalities of genital warts. (10).

<table>
<thead>
<tr>
<th>Treatment type</th>
<th>Description</th>
<th>Mode of action</th>
<th>Administered by</th>
<th>Pregnancy safety</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Topical</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Podophyllotoxin</td>
<td>Antimitotic agent</td>
<td>Induces tissue necrosis</td>
<td>patient</td>
<td>unknown</td>
</tr>
<tr>
<td>Imiquimoid3.75%</td>
<td>Immunomodulatory</td>
<td>Stimulates production of interferon and cytokines</td>
<td>patient</td>
<td>unknown</td>
</tr>
<tr>
<td>Imiquimoid5%(Aldara)</td>
<td>Immunomodulatory</td>
<td>Stimulates production of interferon and cytokines</td>
<td>patient</td>
<td>unknown</td>
</tr>
<tr>
<td>Sinecatechins15% ointment</td>
<td>Botanical extract</td>
<td>Antiviral, immunostimulatory, antiproliferative</td>
<td>patient</td>
<td>unknown</td>
</tr>
<tr>
<td>Podophyllin</td>
<td>Antimitotic agent</td>
<td>Induces tissue necrosis</td>
<td>physician</td>
<td>no</td>
</tr>
<tr>
<td><strong>Destructive and surgical</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tca</td>
<td>Chemically destructive acid</td>
<td>Chemical tissue destruction</td>
<td>physician</td>
<td>yes</td>
</tr>
<tr>
<td>Cryotherapy</td>
<td>Nitrous oxide or liquid nitrogen to “freeze” affected skin tissue</td>
<td>Destruction of affected tissue via freezing</td>
<td>physician</td>
<td>yes</td>
</tr>
<tr>
<td>Electrotherapy</td>
<td>High-frequency electrical currents</td>
<td>Thermal damage</td>
<td>physician</td>
<td>yes</td>
</tr>
<tr>
<td>Surgical excision</td>
<td>Scissor or scalpel excision</td>
<td>Removal of affected tissue</td>
<td>physician</td>
<td>yes</td>
</tr>
<tr>
<td>Co2laser</td>
<td>Infrared light energy</td>
<td>Vaporizes skin cells</td>
<td>physician</td>
<td>yes</td>
</tr>
<tr>
<td><strong>Systemic</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interferon</td>
<td></td>
<td>Interfere with viral replication</td>
<td>physician</td>
<td>no</td>
</tr>
<tr>
<td>Immunotherapy</td>
<td>1-Topical e.g.: Imiquimod 3- Intralesional e.g.: Mumps, Candida 4-systemic e.g.: zinc, interferon</td>
<td>the stimulation of the immune system to deal with the virus and suppress its activity</td>
<td>physician</td>
<td>variable</td>
</tr>
</tbody>
</table>
Patient-Applied Treatments

- **Podophyllotoxin**
  Podophyllotoxin is an antimitotic agent that destroys genital warts by inducing local tissue necrosis. Podophyllotoxin is available as 0.5% solution and 0.15% cream (also available as 0.5% gel in the US); the solution is suitable for penile warts and the cream is more convenient for vulvar and anal warts. Generally, podophyllotoxin is considered to be most suitable for soft, non-keratinized warts. It is recommended that podophyllotoxin is applied twice daily for three consecutive days, followed by a treatment rest of 4–7 days. The application can be repeated for up to four cycles (11). The most commonly reported local adverse effects with podophyllotoxin are burning, local inflammation, itching, pain, erosion, and bleeding. More rarely, balanoposthisis, dyspareunia, scarring, and insomnia have been reported (11).

- **Imiquimod**
  Imiquimod (Aldara) is a heterocyclic imidazoquinoline amide. It is an immune response modifier with antiviral activity. This Toll-like receptor 7 agonist encourages the production of cytokines (IFN-α, TNF-α, and IL-1, 6, 8, 10, and 12), which increase the ability of antigen-presenting cells to present viral antigens to reactive T lymphocytes (11). Imiquimod5% is to be self-applied by the patient three nights per week for up to 16 weeks; if no improvement has been achieved after 4–6 weeks, treatment can be applied daily. In comparison, imiquimod3.75% is self-applied once-nightly for up to 8 weeks (12). Most frequently, local reactions occur and include itching, burning, soreness, pain, flaking, erosions, and crusting. Since it is administered topically; only a small amount of drug should reach systemic circulation, if used properly. However, uncommon systemic side effects have been reported including headache, flu-like symptoms, myalgia, nausea, and fatigue (12).

- **Sinecatechins 15% ointment**
  Sinecatechins (Veregan) is a standardized extract of green tea leaves from *Camellia* sinensis, a species of the Theaceae family, containing chiefly tea polyphenols, particularly catechins (more than 85%). Green tea catechins exert multiple biologic activities, including potent antiviral and antioxidant activity. Catechins bind to a number of proteins, involving enzymes included in the production of inflammatory mediators; proteases promoting tumor invasion; and kinases required in tumor cell signaling, cell cycle modification, and induction of apoptosis (13). Sinecatechins ointment ,Veregan , was approved by the Federal Drug Administration (FDA) in late 2007 for use on external and perianal warts because of their immunomodulatory, antiviral, antioxidative, and antitumor properties (13).
Each 15-g tube of the ointment contains 150 mg of sinecatechins in a water-free ointment base. The ointment is self-applied three times per day to all warts, and it is not essential to wash it off. The application must be continued until complete clearance of warts or up to 16 weeks (13). The most frequent side effects are erythema, pruritis, burning, discomfort/pain, erosion, ulceration, edema, and induration like other topical medications. If these adverse reactions occur, treatment may need to be discontinued the option of restarting after the reaction subsides (13).

Provider-applied treatments: surgical

- **Cryotherapy**
  Cryotherapy utilizes subzero temperature to promote thermo-induced cytolysis (14). Cryotherapy can be delivered by ‘open’ (liquid nitrogen) or ‘closed’ systems. Open application of liquid nitrogen is typically delivered by spray gun device, freezing the lesion and a margin of healthy skin for about 20 s. Closed cryo-probe systems use the circulation of nitrous oxide or carbon dioxide, the probe gently pressed to the surface moistened with saline or lubricating jelly, and freezing is performed until a freezing ‘halo’ occurs a few millimeters around the lesion (14). Cryotherapy can be repeated weekly, biweekly, or every 3 weeks and is a relatively simple, inexpensive technique, demanding minimal training (14).
  The advantages of this treatment option include ease of application, rapid destructive effect, inexpensive and safe in pregnancy. It may have a special advantage in treating bulky keratinized lesions, grouped lesions, and lesions on hair-bearing areas. It only affects tissue to which it is directly applied so it does not have systemic side effects. Following cryosurgery, treated areas need local care only (15).
  Frequent immediate side effects of cryotherapy include exudation, blistering, local destruction of the tissue, painful therapy, ulceration in addition to the late rare complications of hypopigmentation, hyperpigmentation, and scarring (15).

- **Electrosurgery**
  Electrosurgery involves the use of high-frequency electrical currents that burn, excise external genital warts often in a single visit, and then curettage to remove the damaged tissue. It is a painful procedure that usually requires local or general anesthesia (16).
  In the following days, patients may complain about pain, local irritation, and infection at the treatment area. Possible long-term complications include dyschromia or scars/keloids when treating skin lesions in predisposed patients (16).

- **Laser therapy**
  A carbon dioxide (CO₂) laser has been introduced to ablate visible warts. CO₂ lasers wavelength (10600 nm) is highly absorbed by water (primary chromophore for CO₂ laser). The change of radiant energy to heat directly elevates the temperature of the skin water to further than 100 °C; consequently, the tissue water vaporizes. Also, a CO₂ laser ablates and vaporizes the skin wart till normal tissue architecture is seen. The spatial confinement of the laser light allows the exact tissue ablation leading to fast healing with little or no scar tissue (17).
  Laser vaporization is typically used for the treatment of refractory HPV disease or extensive warts of the anogenital mucosal category and is principally useful in the treatment of periurethral and vaginal warts. It is the treatment of choice for pregnant women with extensive warty lesions or lesions that do not respond to TCA. Carbon dioxide laser therapy is an effective therapeutic modality because of its accuracy and rapid healing without scarring (17).
Lasers are risky to the patient, operator, and staff. Extreme caution in their use will almost eliminate the attendant risks of retinal and corneal damage, skin burns, and fire. There has also been expressed concern about probable airborne transmission of viable fragments of papillomavirus, released during laser surgery. Although the practical significance of this finding is unknown, most operators employ strong evacuation in the operative field, to eliminate this hazard. The increased cost of laser therapy is also a limiting factor in using the laser (17).

**Surgical excision**

Surgical excision is one of the oldest documented treatments for the removal of genital warts and is considered for many years to be the primary available option. It involves the physical removal of diseased tissue from the body with scissors or a scalpel, followed by suturing the remaining healthy skin together. It is associated with up to a 72-percent clearance rate, which is obvious immediately and often persisting over a year later. Although now considered to be somewhat outdated, this treatment option is still suitable for very large lesions that may be causing obstruction i.e., involving the urethral meatus, and are unresponsive to other methods of treatment (18).

Surgical removal of large lesions is a painful procedure, which frequently results in bleeding and scar formation. The administration of local or general anesthesia is generally recommended (19). Mohs surgery is a recent surgical excision procedure for the treatment of genital warts. Although intended mainly for cutaneous carcinomas, Mohs is a highly specialized technique in which the skin is removed in very thin layers and subjected to immediate microscopic analysis for traces of pathology. In the continued presence of viral cell features, additional skin slices will be removed until the whole wart is excised and only healthy tissue remains. The obvious advantage of this type of surgery is that it allows for the maximal preservation of healthy skin, resulting in minimal scar formation. However, it is a more expensive and sophisticated process (19).

**Provider-applied treatments: non-surgical**

- **Podophyllin (PD)**
  
  The herbal extract known as podophyllin is a crude, non-standardized, and impure resin preparation gained from the rhizomes of the Podophyllum plant species P peltatum (May apple or mandrake), or P emodi (Indian podophyllum) (20).
  
  Podophyllin is an anti-mitotic and caustic agent with antiviral activity. The probable mechanism of action includes arresting cellular mitosis in metaphase, this is done by the reversal bind to tubuline which is the protein subunit of the spindle microtubules at a site that is the same of overlaps with the colchicines binding site thereby preventing polymerization of tubuline into microtubules. So podophyllin will disturb the cellular cytoskeleton. Also, it blocks oxidation enzymes in tricarboxylic acid cycle, so it will interfere with the nutrition of cells. Furthermore, it inhibits axonal transport, protein, RNA, DNA synthesis, and mitochondrial activity with the reduction of cytochrome oxidase activity (20).
  
  Podophyllin resin is directly applied with a cotton-tipped applicator in the physician’s office to the lesion as a 10–25% solution of PD in a compound tincture of benzoin, washed off 1–4 h later, and repeated once per week for 4–6 weeks. Alternative treatment modalities may be considered if no improvement after this period (20).
  
  Podophyllin is inexpensive, easily obtainable, reliable, physician-applied treatment modality for genital warts. Topical application of a small amount of Podophyllin has been used for the treatment of genital warts since 1942 (21).
PD therapy adverse effects can present as acute toxicity, long-term toxicity, mutagenicity and carcinogenicity, reproductive toxicity, and local toxicity. Local skin reactions are usually seen as erythema, edema, pruritus, burning, tenderness, pain, and intense irritation; rarely erosion, ulceration, and scarring. Systemic toxicity may occur if PD is markedly absorbed into the body. Systemic side effects may include nausea, vomiting, confusion, renal failure, leukopenia, paresthesias, coma, bone marrow depression, teratogenicity, mutagenicity, and death. Therefore, it is contraindicated in pregnancy. PD remains to be used for the treatment of CA because of the easy availability of treatment (21).

To avoid the possibility of systemic complications and toxicity, 1) application should be limited to <0.5 mL of podophyllin or an area of <10 cm² of warts per session; 2) the area to which treatment is applied should not contain any open lesions, wounds, or friable tissue; and 3) the preparation should be carefully washed off 1–4 hours after application (21).

- **Trichloroacetic acid (TCA)**
  TCA is a caustic agent that results in tissue necrosis and lesion eradication by the chemical coagulation of cellular proteins. It is applied as 80–90% solution directly to the warty tissue (22). It is directly applied to the wart surface with a cotton-tip applicator and after it dries a white frosting will appear. Healthy surrounding tissue can be protected by the application of petroleum jelly and excess medication can be neutralized with talc, sodium bicarbonate, or washed with liquid soap. It is administrated weekly for six weeks or until lesions disappear (22).
  
  TCA is the preferred treatment for small-medium size mucosal warts and intracavitary warts (vagina, rectum). It is a safe and effective treatment in the first half of pregnancy (22).
  
  TCA adverse effects include pain, burning during the application, and, after that, ulceration and destruction of surrounding skin tissue, but no permanent scarring (22).

**Therapies Not Currently Recommended**

- **Interferons (IFNs)**
  Viral-infected keratinocytes produce interferon-alpha, which inhibits viral replication. Systemic and Intrallesional IFNs are proinflammatory cytokines that have broad antiviral effects. Grassegger & Hüpfl (23) However, various studies have failed to demonstrate a clear benefit of interferon-alpha injections compared to placebo. Additionally, most patients treated develop flu-like symptoms in a dose-dependent manner (24).

- **Cidofovir**
  Cidofovir is a potent antiviral that suppresses the activity of viral DNA polymerase and that has been approved for the intravenous treatment of retinitis due to cytomegalovirus in immunosuppressed patients. It has also been used (off label) for the topical treatment of viral warts, mostly in immunocompromised patients (25).
References


