

## REVIEW

### Penile warts: an update on their evaluation and management

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#### Abstract

**Background:** Penile warts are the most common sexually transmitted disease in males. Clinicians should be familiar with the proper evaluation and management of this common condition.

**Objective:** To provide an update on the current understanding, evaluation, and management of penile warts.

**Methods:** A PubMed search was completed in Clinical Queries using the key terms 'penile warts' and 'genital warts'. The search strategy included meta-analyses, randomized controlled trials, clinical trials, observational studies, and reviews.

**Results:** Penile warts are caused by human papillomavirus (HPV), notably HPV-6 and HPV-11. Penile warts typically present as asymptomatic papules or plaques. Lesions may be filiform, exophytic, papillomatous, verrucous, hyperkeratotic, cerebriform, fungating, or cauliflower-like. Approximately one-third of penile warts regress without treatment and the average duration prior to resolution is approximately 9 months. Active treatment is preferable to watchful observation to speed up clearance of the lesions and to assuage fears of transmission and autoinoculation. Patient-administered therapies include podoflox (0.5%) solution or gel, imiquimod 3.75 or 5% cream, and sinecatechins (polypheron E) 15% ointment. Clinician-

administered therapies include podophyllin, cryotherapy, bichloroacetic or trichloroacetic acid, oral cimetidine, surgical excision, electrocautery, and carbon dioxide laser therapy. Patients who do not respond to first-line treatments may respond to other therapies or a combination of treatment modalities. Second-line therapies include topical/intralesional/intravenous cidofovir, topical 5-fluorouracil, and topical ingenol mebutate.

**Conclusion:** No single treatment has been shown to be consistently superior to other treatment modalities. The choice of the treatment method should depend on the physician's comfort level with the various treatment options, the patient's preference and tolerability of treatment, and the number and severity of lesions. The comparative efficacy, ease of administration, adverse effects, cost, and availability of the treatment modality should also be taken into consideration.

**Keywords:** bichloroacetic/trichloroacetic acid, cimetidine, cryotherapy, electrocautery, human papillomavirus, imiquimod, laser, podoflox, podophyllin, sinecatechins, surgery.

#### Citation

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## Introduction

Penile warts are the most common sexually transmitted disease in males and are caused by human papillomavirus (HPV).<sup>1-3</sup> Penile warts typically present as soft flesh-colored to brown papules or plaques on the penile shaft and glans penis.<sup>4</sup>

To provide an update on the current understanding, evaluation, and management of penile warts, a narrative review was conducted based on a PubMed search using the key terms 'penile warts' and 'genital warts'. The search strategy included

meta-analyses, randomized controlled trials, clinical trials, observation studies, and reviews.

## Epidemiology

Worldwide, HPV infection is the most common sexually transmitted disease.<sup>4</sup> In the United States, 50–75% of sexually active individuals have been infected with genital HPV at some point during their lifetime.<sup>4,5</sup> Infection with genital HPV does not mean that an individual will develop genital warts.<sup>5</sup> It is

estimated that 0.5–5% of sexually active young male adults have genital warts upon physical examination.<sup>6–9</sup> The peak age is between 25 and 29 years.<sup>7,10</sup> Generally, approximately 75% of males who have sexual contact with a partner who has genital warts develop penile warts within 8 months.<sup>8</sup>

## Etiopathogenesis

HPV is a nonenveloped, capsid, double-stranded deoxyribonucleic acid (DNA) virus belonging to the *Papillomavirus* genus of the Papillomaviridae family and infects only humans.<sup>11</sup> The virus has an eight kilobase circular genome that encodes eight genes, including the genes for the two encapsulating structural proteins, namely L1 and L2.<sup>11</sup> The virus-like particle containing L1 is used in the manufacturing of HPV vaccines.<sup>11</sup> L1 and L2 mediate HPV infectivity.<sup>11</sup>

More than 200 HPV types have been isolated thus far, of which more than 100 HPV genotypes have been sequenced.<sup>4,11,12</sup> More than 40 HPV types can be transmitted sexually.<sup>4,11,12</sup> HPV can be divided into high-risk or low-risk types based on their risk for cancer. Approximately 90% of genital warts are caused by the low-risk types HPV-6 and/or HPV-11.<sup>2–4,13</sup> HPV-1, HPV-2, HPV-3, HPV-4, HPV-16, HPV-18, HPV-40, HPV-42, HPV-43, HPV-44, HPV-54, HPV-70, HPV-72, and HPV-81 account for the rest.<sup>14</sup> It is possible to be infected with different HPV types at the same time.<sup>8</sup> In adults, genital HPV infection is predominately transmitted by sexual intercourse and, less commonly, by oral sex, skin-to-skin transmission, and fomites.<sup>8</sup> In children, HPV infection may result from sexual abuse, vertical transmission, autoinoculation, hetero-inoculation (nonsexual contact with a caregiver), and transmission via fomites.<sup>1,15</sup> The HPV virus invades cells in the basal layer of the epidermis through micro-abrasions in the skin or mucosa.<sup>13</sup> The incubation period for genital infection varies from 3 weeks to 8 months, with an average of 2–4 months.<sup>12,16,17</sup> The disease is more common in individuals with the following factors: immunodeficiency, unprotected sexual intercourse, multiple sexual partners, sexual partner with multiple sexual partners, prior sexually transmitted disease, sexual intercourse at an early age, shorter time interval between meeting with a new partner and engaging in sexual activity, non-circumcision, and smoking.<sup>3,18–21</sup> Moisture, maceration, trauma, and epithelial defects in the penile area are other predisposing factors.<sup>3</sup>

## Histopathology

Histological findings include papillomatosis, focal parakeratosis, marked acanthosis, multiple vacuolated koilocytes, vascular distension, and coarse keratohyalin granules.<sup>4,17</sup>

## Clinical manifestations

Penile warts are usually asymptomatic and rarely pruritic or painful.<sup>3,8,13</sup> Penile warts are usually located on the frenulum, glans penis, inner surface of the prepuce, and coronal

**Figure 1. Penile warts manifesting as small, discrete, soft, smooth, flesh-colored, dome-shaped papules.**



**Figure 2. Penile warts manifesting as multiple, small, discrete, soft, smooth, flesh-colored, dome-shaped papules in clusters.**



sulcus.<sup>3,8,13</sup> Penile warts typically present as small, discrete, soft, smooth, pearly, dome-shaped papules at onset.<sup>3,7,14</sup> Lesions can occur separately (Figure 1) or in clusters (Figure 2).<sup>8</sup> They can be pedunculated or sessile. With time, the papules may coalesce into plaques.<sup>14</sup> Lesions may be filiform, exophytic, papillomatous, verrucous, hyperkeratotic, cerebriform, fungating, or cauliflower-like (Figures 3–5).<sup>3,7,22</sup> The color is variable and may be flesh-colored, pink, erythematous, brown, violaceous, or hyperpigmented.<sup>4,23</sup>

## Diagnosis

The diagnosis is mainly clinical, based on the history and physical findings. Dermoscopy and *in vivo* reflectance confocal microscopy help to increase the diagnostic accuracy.<sup>24</sup> The

**Figure 3. Penile warts manifesting as multiple verrucous papules and plaques.**



**Figure 5. Penile warts manifesting as papillomas on the penile shaft.**



**Figure 4. Penile warts that are cauliflower-like.**



## Differential diagnosis

Differential diagnosis includes pearly penile papules, Fordyce spots, acrochordons, condylomata lata of syphilis, molluscum contagiosum, granuloma annulare, lichen nitidus, lichen planus, seborrheic keratosis, epidermal nevus, lymphangioma circumscriptum, lymphogranuloma venereum, scabies, syringomas, traumatic neuromas, schwannomas, bowenoid papulosis, and squamous cell carcinoma.<sup>7</sup>

Pearly penile papules typically present as asymptomatic, small, smooth, soft, yellowish, pearly white, or flesh-colored, conical- or dome-shaped papules 1–4 mm in diameter (Figure 6).<sup>27</sup> The lesions are usually uniform in size and shape and are symmetrically distributed.<sup>27</sup> Typically, the papules occur in single, double, or multiple rows circumferentially around the corona and sulcus of the glans penis. The papules tend to be more prominent on the dorsum of the corona and less prominent towards the frenulum.<sup>27</sup>

Fordyce spots are enlarged sebaceous glands. On the glans and shaft of the penis, Fordyce spots appear as asymptomatic, isolated or grouped, discrete, creamy yellow, smooth papules 1–2 mm in diameter (Figure 7).<sup>28–30</sup> On the penile shaft, these papules are more obvious during penile erection or when the foreskin is stretched.<sup>28,30</sup> A thick chalky or cheesy material can sometimes be expressed by squeezing the lesion.<sup>28</sup>

Acrochordons, also known as skin tags, are soft, flesh-colored to dark brown, sessile or pedunculated skin growths with a smooth contour (Figure 8).<sup>31,32</sup> Occasionally, the lesions may be hyperkeratotic or have a warty appearance.<sup>33</sup> Most acrochordons are 2–5 mm in diameter, although often larger in the groin.<sup>32</sup> They can appear in almost any part of the body but are more frequently seen on the neck and intertriginous areas.<sup>31,32</sup> When they occur on the penile area, they can mimic penile warts.

morphological features may vary from finger-like, knob-like, to mosaic-like pattern.<sup>24–26</sup> Among the vascular features, glomerular, hairpin, and dotted vessels are commonly seen.<sup>26</sup> Papillomatosis is a constant feature.<sup>4</sup> Some authors suggest the use of acetowhite test to aid the diagnosis of penile warts. While the sensitivity of acetowhite test is high for hyperplastic penile warts, the sensitivity is low for other types of penile warts and subclinically infected areas. Skin biopsy is seldom warranted but should be considered for atypical features (e.g., atypical pigmentation, induration, fixation to underlying structures, hard consistency, ulceration, or bleeding), when the diagnosis is in doubt or for warts recalcitrant to various treatment modalities. Although some authors suggest HPV DNA test to show the type of HPV that may affect the risk of malignant transformation, HPV typing is generally not recommended for routine diagnosis and not easily obtained.<sup>13</sup>

**Figure 6.** Pearly penile papules presenting as flesh-colored papules circumferentially distributed on the corona of the glans penis.



**Figure 7.** Fordyce spots presenting as discrete, creamy yellow, smooth papules.



**Figure 8.** Acrochordons presenting as soft, flesh-colored skin growths with a smooth contour.



**Figure 9.** Molluscum contagiosum presents as discrete, smooth, dome-shaped, pearly white papules on the penile shaft.

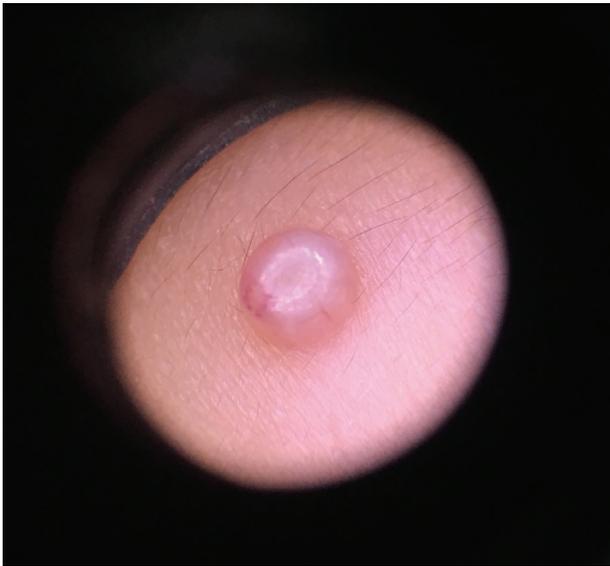


sites of the genitals and perineum.<sup>36</sup> A nonpruritic, diffuse, symmetrical, maculopapular rash on the trunk, palms, and soles is characteristic of secondary syphilis.<sup>34</sup> Systemic manifestations include headache, fatigue, pharyngitis, myalgia, and arthralgia.<sup>34</sup> Alopecia, erythematous, or leukoplakic lesions on the oral mucosa and generalized lymphadenopathy may be present.<sup>36</sup>

Typically, molluscum contagiosum presents as discrete, smooth, firm, dome-shaped, yellow, pearly white or skin-colored, waxy papules with characteristic central umbilication (Figures 9 and 10).<sup>37-39</sup> In the pediatric age group, lesions are most commonly seen on the trunk and intertriginous areas, whereas in adults, lesions are more commonly seen on the lower abdomen, upper thighs, and genital area (Figure 9).<sup>39</sup> The size of lesions ranges from 1 to 5 mm in diameter and the number of lesions is usually less than 20.<sup>38,39</sup>

Condylomata lata or condyloma latum are cutaneous lesions of secondary syphilis caused by the spirochete, *Treponema pallidum*.<sup>34,35</sup> Clinically, condylomata lata manifest as moist, gray-white, velvety, flat-topped or cauliflower-like, broad papules or plaques.<sup>36</sup> They tend to develop in warm, moist

**Figure 10.** Examination of a molluscum contagiosum lesion under a dermatoscope shows a discrete dome-shaped papule with central umbilication.



**Figure 11.** Lichen nitidus presenting as multiple discrete, flat-topped, flesh-colored papules on the penile shaft.



Granuloma annulare is a benign, self-limited inflammatory disease of the dermis and subcutaneous tissue. The condition is characterized by asymptomatic, firm, brown violaceous, erythematous, or flesh-colored papules, typically arranged in an annular, circinate configuration.<sup>40</sup> As the condition progresses, central involution may be noted.<sup>40</sup> The ring of papules often becomes coalescent to form an annular plaque. Granuloma annulare typically involves the extensor surfaces of the distal extremities but may also involve the shaft and glans of the penis.<sup>41,42</sup>

**Figure 12.** Lichen planus presenting as purple, planar, polygonal papules on the glans penis.



**Figure 13.** Seborrheic keratosis presenting as a well-demarcated, oval, brown plaque with a 'stuck on' warty appearance.



Lichen nitidus is a chronic inflammatory dermatosis characterized by numerous, asymptomatic, discrete, flat-topped, flesh-colored, shiny, pinhead- to pinpoint-sized papules (Figure 11).<sup>43,44</sup> The abdomen, chest, extremities, and penis are sites of predilection.<sup>43–45</sup> The lesions are usually arranged in groups.<sup>43</sup>

Cutaneous lichen planus is a chronic inflammatory dermatosis characterized by six Ps: pruritic, purple (violaceous), planar (flat-topped), polygonal, papules/plaques that affect the skin (Figure 12).<sup>46</sup> Sites of predilection include the flexor aspects of the wrists, dorsa of hands, trunk, shins, ankles, and glans penis.<sup>47</sup> Approximately 25% of the lesions occur on the genitalia.<sup>47</sup>

Seborrheic keratosis typically presents as an asymptomatic, well-demarcated, round or oval, brown plaque with a 'stuck on' warty appearance (Figure 13).<sup>48</sup> Often, lesions may appear

**Figure 14. Lymphangioma circumscriptum presenting as clusters of small firm dark-red blisters with warty surface on the distal penis, resembling frog spawn.**



**Figure 15. Human scabies presenting as erythematous papules, which are intensely pruritic.**



shiny and oily and, hence, the misnomer 'seborrheic' (greasy) keratosis.<sup>48</sup> Sites of predilection include the face, chest, back, and extremities. Occurrence on the penis is rare but has been reported.<sup>49</sup> HPV is found in approximately 70% of cases of seborrheic keratosis in the genital area versus 5% in nongenital areas.<sup>49</sup>

An epidermal nevus is a hamartoma arising from embryonic ectoderm that differentiates into keratinocytes, apocrine glands, eccrine glands, hair follicles, and sebaceous glands. The classic lesion is a solitary, asymptomatic, well-circumscribed plaque that follows Blaschko lines. The onset is usually within the first year of life. The color varies from flesh to yellow to brown. The lesion may thicken and become more verrucous with time.

Lymphangioma circumscriptum is a benign saccular dilatation of the cutaneous and subcutaneous lymphatics.<sup>50</sup> The condition is characterized by clusters of vesicles resembling frog spawn (Figure 14). The color depends on the content: whitish, yellow, or light tan coloration is due to color of the lymph fluid while reddish or blue color is due to the presence of erythrocytes in the lymph fluid as a result of hemorrhage.<sup>51</sup> The vesicles may undergo verrucous changes and have a warty appearance.<sup>50</sup> Sites of predilection include the extremities and, less commonly, the genitalia.<sup>52</sup>

Lymphogranuloma venereum is a sexually transmitted disease caused by *Chlamydia trachomatis*.<sup>34</sup> The condition is characterized by a transient painless genital papule and, less commonly, an erosion, ulcer, or pustule followed by inguinal and/or femoral lymphadenopathy with a characteristic 'groove sign' known as buboes.<sup>34,53</sup>

Human scabies, caused by the parasite mite *Sarcoptes scabiei var hominis*, is characterized by burrows, erythematous papular eruption, and intense pruritus (often worse at night).<sup>54</sup> The papules, caused by a hypersensitivity reaction to the mite, are erythematous and usually 1–2 mm in diameter (Figure 15).<sup>54</sup>

Typically, syringomas present as asymptomatic, small, soft to firm, flesh- to tan-colored papules usually 1–3 mm in diameter.<sup>55</sup> The lesions are usually found in the periorbital areas and on the upper cheeks.<sup>55</sup> However, syringomas may appear on the penis and buttocks. When located on the penis, syringomas may be mistaken for penile warts.

Traumatic neuromas are nerve sheath tumors in which the ratio of axons to Schwann cell fascicles is approximately equal.<sup>56,57</sup> The condition results from regenerative proliferation of traumatized or injured nerve fibers.<sup>56,57</sup> Penile traumatic neuromas may result from trauma to the penis, such as circumcision or penile dorsal neurotomy to treat premature ejaculation.<sup>56–59</sup> Clinically, penile traumatic neuromas present with skin-colored or erythematous papules or nodules on the glans or penile shaft.<sup>56–59</sup>

Schwannomas are neoplasms originated from Schwann cells.<sup>60</sup> A penile schwannoma typically presents as a solitary,

asymptomatic, slow-growing nodule on the dorsal aspect of the penile shaft.<sup>60,61</sup>

Bowenoid papulosis is a premalignant focal intraepidermal dysplasia that typically manifests as multiple red to brown papules or plaques in the anogenital area, such as the penis.<sup>62</sup> The condition corresponds to *in situ* squamous cell carcinoma. Progression to invasive squamous cell carcinoma occurs in 2–3% of cases.<sup>62</sup>

Typically, squamous cell carcinoma of the penis presents as a nodule, ulcer, or erythematous lesion.<sup>63</sup> The lesion may appear warty, leukoplakic, or sclerotic.<sup>63,64</sup> The most common site is the glans penis, followed by the prepuce and shaft.<sup>63</sup>

## Complications

Penile warts can be a cause of significant anxiety or distress to the patient and his sexual partner because of their disfiguring appearance and transmissibility, stigmatization, concerns about future fertility and risk of cancer, and their association with other sexually transmitted diseases.<sup>65,66</sup> It is estimated that 20–34% of affected patients have concomitant sexually transmitted diseases.<sup>17</sup> Affected patients often experience guilt, feelings of shame, low self-esteem, and angst.<sup>67</sup> Individuals with penile warts have higher rates of sexual dysfunction, depression, and anxiety when compared with the normal population.<sup>65,68</sup> The condition can have negative psychosocial effects on the patient and may adversely affect quality of life.<sup>66,69–72</sup> Large exophytic lesions may bleed, cause urethral obstruction, and interfere with sexual intercourse.<sup>7,14,73</sup> Malignant transformation is rare except in immunocompromised individuals.<sup>74,75</sup> Individuals with penile warts are at increased risk for anogenital, head, and neck cancers as a result of coinfection with high-risk HPV genotypes.<sup>4,76</sup>

## Prognosis

If left untreated, penile warts may resolve spontaneously, stay the same, or increase in size and number.<sup>3</sup> Approximately one-third of penile warts regress without treatment and the average duration prior to resolution is approximately 9 months.<sup>4,77</sup> Proper treatment has a clearance rate of 35–100% in 3–16 weeks.<sup>65</sup> In spite of resolution of visible warts, HPV infection may persist and may result in recurrence of penile warts.<sup>4</sup> The recurrence rate ranges from 25 to 67% within 6 months of treatment.<sup>7,78</sup> Patients with subclinical infection, recurrent infection from sexual contact, and immunodeficiency have higher recurrence rate.<sup>79</sup>

## Management

Active treatment of penile warts is preferable to watchful observation to speed up clearance of the lesions, assuage fears of transmission and autoinoculation, allay emotional stress, improve cosmetic appearance, reduce social stigma associated

with penile lesions, and alleviate symptoms (e.g., pruritus, pain, or bleeding).<sup>3,7,77</sup> Penile warts that persist for more than 2 years are less likely to resolve spontaneously and active treatment should be seriously considered.<sup>14</sup> Sexual partners should be offered informational counseling. Testing for other sexually transmitted diseases is advisable.

Active treatments may be mechanical, chemical, immunomodulatory, and antiviral.<sup>80</sup> Head-to-head comparisons of available modalities are scarce. Effectiveness varies among treatment modalities. Thus far, no single treatment has been shown to be consistently superior to other treatment modalities. The choice of the treatment method should depend on the physician's comfort level with the various treatment options, the patient's preference and tolerability of treatment, and the number and severity of lesions. The comparative efficacy, ease of administration, adverse effects, cost, and availability of the treatment modality should also be taken into consideration. In general, patient-administered therapies are less effective compared with clinician-administered ones.<sup>6</sup>

## Patient-administered therapies

Patient-administered therapies include podofilox (0.5%) solution or gel, imiquimod 3.75 or 5% cream, and sinecatechins (polypheron E) 15% ointment.<sup>13,80,81</sup> Podofilox (0.5%) solution or gel is derived from podophyllotoxin, a plant resin that works by disrupting microtubules during cell cycle replication, arresting mitosis, and causing tissue necrosis, and has been shown efficacious in the treatment of penile warts.<sup>79,82</sup> Podofilox (0.5%) solution or gel is applied topically twice a day for 3 consecutive days per week and can be applied at home.<sup>7</sup> The weekly cycle can be repeated up to four times.<sup>7</sup> Clearance rates range from 45 to 77%.<sup>7</sup> Adverse events include local discomfort, pruritus, irritation, burning, pain, xerosis, erythema, erosion, ulceration, and postinflammatory pigmentary changes at the site of application.<sup>7,14</sup> To minimize local adverse events, podophyllotoxin should be washed off 1–4 hours after application.<sup>79</sup> Sexual intercourse should be avoided when podophyllotoxin is still on the skin.<sup>79</sup>

Imiquimod is available as 3.75 and 5% cream. Imiquimod enhances the host's innate and cellular immune response and combats HPV infection by binding to the dermal dendritic cells and macrophages through toll-like receptor-7.<sup>9</sup> This results in the production and release of proinflammatory cytokines, such as interferon alpha (IFN- $\alpha$ ), tumor necrosis factor alpha (TNF- $\alpha$ ), and interleukin (IL)-1, IL-6, IL-8, and IL-12.<sup>7,79</sup> The secreted cytokines stimulate local immune effects that are cytotoxic against HPV. Imiquimod also acts on cell-mediated immunity by activating Langerhans cells, thereby increasing the presentation of antigens for the T cells. Studies have shown that topical application of 5% imiquimod cream is beneficial in the treatment of penile warts.<sup>83</sup> The 5% imiquimod is applied three times per week till total clearance of the lesion or for a

maximum of 16 weeks, while the 3.75% imiquimod is applied nightly for up to 8 weeks.<sup>9,79</sup> Clearance rates are similar to those of podofilox.<sup>7</sup> Adverse events with topical imiquimod include local irritation, pruritus, burning, erythema, vesicles, erosions, ulceration, and hypopigmentation at the application site and, less frequently, flu-like symptoms.<sup>14,79</sup> To minimize local adverse events, the treatment area should be washed with soap and water 6–10 hours after application.

Sinecatechins ointment is a water extract of leaves of green tea (*Camellia sinensis*) and available as 10 and 15% formulations. It is believed that the medication works by decreasing viral replication through upregulation of apoptosis-associated genes and modulation of genes involved in the proinflammatory response to HPV infection.<sup>7,79</sup> Sinecatechins ointment is a safe and effective treatment of penile warts in immunocompetent males aged 18 years and older.<sup>13,84</sup> It is recommended that sinecatechins ointment be applied three times a day for up to 16 weeks.<sup>6,7</sup> It is not necessary to wash the ointment off prior to the next application.<sup>6</sup> Two randomized, double-blind, phase III trials (n=1005) showed rates of complete clearance and recurrence after 12 weeks of genital warts were significantly superior to the control group ( $p < 0.001$  and  $p < 0.001$ , respectively).<sup>6</sup> Adverse effects include pruritus, burning, discomfort, irritation, pain, erythema, edema, induration, vesicular rash, erosion, and ulceration at the application site, which occur in approximately 20% of patients.<sup>6,7,13</sup> Staining of underwear is another nuisance aspect. A single-blind, randomized controlled trial (n=42) showed that cryotherapy plus sinecatechins 15% ointment was more effective in the treatment of external genital warts compared to cryotherapy alone (–5.0 lesions versus –2.1 lesions, respectively,  $p = 0.07$ ).<sup>85</sup>

## Clinician-administered therapies

Clinician-administered therapies include podophyllin, cryotherapy with liquid nitrogen, bichloroacetic or trichloroacetic acid, oral cimetidine, surgical excision, electrocautery, and carbon dioxide laser therapy.<sup>80,81</sup> Podophyllin 25% liquid, derived from podophyllotoxin, works by arresting mitosis and causing tissue necrosis.<sup>7</sup> The medication is applied directly to the penile wart once a week for up to 6 weeks, with a maximum of 0.5 ml per treatment.<sup>7</sup> Podophyllin 25% liquid should be washed off 1–4 hours post-treatment and should not be applied to any raw area.<sup>7</sup> The clearance rate is approximately 62%.<sup>7</sup> Because of the reported toxicity including death associated with its use, podofilox, its purified form, is preferred, which has a much better safety profile.<sup>7</sup>

Liquid nitrogen, a treatment of choice for penile warts, can be applied via a spray gun or a cotton-tip applicator directly to and 2 mm surrounding the lesion.<sup>79</sup> Liquid nitrogen works by causing tissue damage and cell death through rapid freezing with formation of ice crystals.<sup>79,86</sup> The minimum temperature required for destruction of the warts is –50°C, although some authors believe that a temperature of –20°C is also effective.<sup>86</sup>

The success rate is about 75%.<sup>79</sup> Adverse effects include pain during treatment, erythema, peeling, vesicle, erosion, ulceration, and dyspigmentation at the application site.<sup>82</sup> A recent phase II parallel-randomized study on 16 Iranian men with genital warts showed that cryotherapy using Wartner compound that contains a mixture of 75% of dimethyl ether and 25% of propane is also effective. Further studies need to be done to confirm or refute this finding.<sup>86</sup> Suffice to say, cryotherapy using Wartner compound is less effective than cryotherapy using liquid nitrogen.<sup>86</sup>

Bichloroacetic and trichloroacetic acid can be used for the treatment of small penile warts, as their ability to penetrate skin is limited.<sup>79</sup> Either medication works by protein coagulation with resultant cell destruction and eradication of the penile wart.<sup>7</sup> A burning sensation may be experienced at the application site. Recurrences following the application of bichloroacetic or trichloroacetic acid are common. The medication can be applied up to three times weekly.<sup>7</sup> Clearance rates range from 64 to 88%.<sup>7</sup>

Oral cimetidine, a H<sub>2</sub>-receptor antagonist, presumably works by enhancing cell-mediated immunity against HPV.<sup>87</sup> The recommended dose is 25–40 mg/kg/day. The medication is safe, painless, and well tolerated.<sup>88</sup>

Electrocautery, pulsed dye laser therapy, carbon dioxide laser therapy, or surgical excision works by mechanical destruction of the penile wart, and they may be required if the lesion is extensive, bulky, or recalcitrant to conservative treatment.<sup>14,79,89,90</sup> These modalities of treatment have the highest success rate but also have the potential of leaving scars on the skin. Topical anesthesia, such as with Nanorap (a hydrogel with 2.5% lidocaine and 2.5% prilocaine with 50% of active products in nanocapsules) applied over the lesions without occlusion 20 minutes before the procedure or a eutectic mixture of local anesthetics (EMLA) applied over the lesions with occlusion for an hour before the procedure, should be considered to reduce the discomfort/pain, which can be disturbing for some individuals.<sup>44</sup> General anesthesia may be necessary for surgical removal of large and extensive lesions.

## Alternate therapies

Patients who do not respond to first-line treatments may respond to other therapies or a combination of treatment modalities.<sup>75,79</sup> Second-line therapies include topical/intralesional/intravenous cidofovir, topical 5-fluorouracil, and topical ingenol mebutate.

Antiviral therapy with topical, intralesional, or intravenous cidofovir may be considered for immunocompromised patients with severe, refractory lesions.<sup>14</sup> Cidofovir is an acyclic nucleoside phosphonate that competitively inhibits viral DNA polymerase, thereby preventing viral replication.<sup>79,91</sup> Adverse effects of topical or intralesional cidofovir include irritation, erosion, post-inflammatory pigmentary changes, and superficial scars at the site of application.<sup>88</sup> The main adverse

effect of intravenous cidofovir is nephrotoxicity, which can be prevented by saline hydration and probenecid.<sup>91</sup>

Topical 5-fluorouracil has been shown to be effective in the treatment of penile warts.<sup>92</sup> 5-fluorouracil is an antimetabolite fluoropyrimidine analog of the nucleoside pyrimidine. The medication works by blocking the action of thymidylate synthase and thereby stopping the production of DNA. A Cochrane database systematic review of six randomized, placebo-controlled trials involving 988 patients with genital warts showed that topical 5-fluorouracil was more effective than no treatment or placebo (relative risk: 0.39; 95% confidence interval: 0.23–0.67).<sup>92</sup> The authors cautioned that further studies are necessary due to lack of high-quality randomized, placebo-controlled trials.<sup>92</sup> Adverse events of topical 5-fluorouracil include pain, burning, inflammation, and ulceration at the application site.<sup>79</sup>

Preliminary studies showed that topical application of ingenol mebutate gel is efficacious in the treatment of genital warts.<sup>93–95</sup> Ingenol mebutate works by induction of cell death in proliferating keratinocytes and by stimulation of an inflammatory response characterized by infiltration of neutrophils.<sup>95</sup> Local skin irritation may occur after 24–48 hours.<sup>94,95</sup> The recurrence rate is unknown.

## Prevention

Genital warts can be prevented, to a certain extent, by delaying sexual initiation and limiting the number of sexual partners.<sup>3</sup> Latex condoms, when used consistently and properly, reduce HPV transmission. Sexual partners with anogenital warts should be treated.

HPV vaccines prior to the onset of sexual activity are effective in the primary prevention of HPV infection.<sup>5</sup> This is because the vaccines do not provide protection against diseases from vaccine HPV types that the individual has acquired through prior sexual activity.<sup>96</sup> The Advisory Committee on Immunization Practices of the Centers for Disease Control and Prevention, the American Academy of Pediatrics, the American College of Obstetricians and Gynecologists, the American Academy of Family Practice, and the International Papillomavirus Society recommend routine vaccination with HPV vaccine for girls and boys.<sup>81,97–101</sup> The target age for vaccination is 11–12 years for girls and boys.<sup>100–102</sup> The vaccine can be administered as early as 9 years of age.<sup>97</sup> Three doses of HPV vaccine should be given at 0, 1–2 (typically 2), and 6 months.<sup>97</sup> Catch-up vaccination is indicated for males through age 21 years and females through age 26 years if not vaccinated

in the target age.<sup>99–102</sup> Vaccination is also recommended for men who are homosexual or immunocompromised through age 26 years if not vaccinated before.<sup>100,101</sup> HPV vaccination reduces the chance of HPV infection and subsequent penile warts as well as penile cancers. Vaccinating both males and females is more beneficial in reducing penile warts than by vaccinating only males, as males may acquire HPV infection from their female sexual partners. The prevalence of anogenital warts decreased significantly from 2008 to 2014, thanks to the administration of the HPV vaccine.<sup>103</sup> The annual percentage change among males aged 20–24 years was –6% ( $p=0.005$ ).<sup>103</sup> The decreased prevalence likely results from herd protection from vaccination among females. A 2017 systematic review and meta-analysis of six studies ( $n=27,078$ ) showed that HPV quadrivalent vaccine is efficacious in preventing anogenital warts in both males and females.<sup>104</sup> The 9-valent vaccine (Gardasil-9) which has replaced the 4-valent vaccine (Gardasil) targets HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58 and contains those virus-like particles.<sup>96,101,105</sup> As such, the 9-valent vaccine is effective in the prevention of penile warts.<sup>105</sup> The bivalent vaccine (Cervarix) targets only HPV types 16 and 18 and is not effective in the prevention of penile warts.<sup>97</sup> Safety data for the HPV vaccines are reassuring.<sup>102</sup>

## Conclusion

Penile warts are sexually transmitted disease caused by HPV. The condition can have negative psychosocial effects on the patient and may adversely affect quality of life. Although approximately one-third of penile warts regress without treatment, active treatment is preferred to speed up clearance of the lesions, assuage fears of transmission and autoinoculation, allay emotional stress, improve cosmetic appearance, reduce social stigma associated with penile lesions, and alleviate symptoms. Active treatments may be mechanical, chemical, immunomodulatory, and antiviral, and often a combination of these. Thus far, no single treatment has been shown to be consistently superior to other treatment modalities. The choice of the treatment method should depend on the physician's comfort level with the various treatment options, the patient's preference and tolerability of treatment, and the number and severity of lesions. The comparative efficacy, ease of use, adverse effects, cost, and availability of the treatment modality should also be taken into consideration. HPV vaccines prior to the onset of sexual activity are effective in the primary prevention of HPV infection. The target age for vaccination is 11–12 years for both girls and boys.

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