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## Childhood Warts: An Update

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*Warts are benign intraepidermal neoplasms that are caused by infection with human papillomavirus and commonly affect children and adolescents. The 4 most common types of cutaneous warts are common warts, plantar warts, flat warts, and genital warts. Although they rarely pose a serious health problem, warts can result in physical impairment and psychosocial discomfort. A variety of treatment modalities are employed to treat these growths in children.*

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**W**arts are benign intraepidermal tumors that arise on both skin and mucosal surfaces and occur commonly in children. Warts affect approximately 10% of children and adolescents, with the peak incidence occurring between the ages of 9 and 16 years.<sup>1-3</sup> The 4 most common types of cutaneous warts are the common wart (*verruca vulgaris*), plantar wart (*verruca plantaris*), flat wart (*verruca plana*), and genital wart (*condyloma acuminatum*). Although these lesions rarely pose a serious health problem, they can result in significant physical impairment and psychosocial discomfort. Many treatment modalities are used to treat warts in children, but no particular treatment is universally efficacious. Thus, warts continue to pose a therapeutic challenge.

### Clinical Manifestations

Common warts occur most frequently on the dorsal aspect of the hands (favoring the fingers and periungual region) and on the palms (Figure 1). They can, however, occur anywhere on the body and on mucosal surfaces. Typically, they begin as discrete,

pinpoint, flesh-colored papules. Over weeks to months, they enlarge into yellow, black, or brown papules with a rough papillomatous surface. Common warts range from a single lesion to multiple coalescing lesions. Periungual warts, particularly common in individuals with habitual nail biting or cuticle manipulation, often become irritated or infected. Incomplete treatment or irritation may lead to autoinoculation and the development of satellite lesions surrounding the original wart. Digitate and filiform warts, variants of common warts, tend to occur on the face and scalp, presenting as single or multiple spikes protruding from the skin surface. The diagnosis of common warts can be easily confirmed by gently paring the lesion with a 15 blade to reveal characteristic black dots, which represent thrombosed capillaries.

Plantar warts occur on the plantar surfaces of the weight-bearing regions of the toes, mid-metatarsals, and heels. The constant, repetitive pressure induced by ambulation often causes the warts to become very deep-seated and painful. Plantar warts may be multiple, with the development of smaller satellite lesions. The term *mosaic warts* refers to multiple, contiguous plantar warts fusing to form a thick keratotic plaque. The differential diagnosis of plantar warts includes calluses, corns, and talon noir (black heel). However, paring with a 15 blade may be done to differentiate plantar warts from these lesions.

Flat warts occur most commonly on the face, neck, and extremities. They present as flat-topped smooth papules ranging from 2 to 5 mm in diameter and are flesh-colored, erythematous to brown, or hyperpigmented (Figure 2). Two to several hundred lesions may develop. Shaving, especially in the beard area in men and legs in women, leads to autoinoculation and subsequent spread of lesions. A linear array of lesions, due to the Köbner phenomenon, is characteristic. At times, flat warts may resemble other lesions. Hyperpigmented flat warts may be mistaken for lentiginos or ephelides.

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Plaques of coalescing flat warts must be differentiated from lichen planus and molluscum contagiosum. In addition, erythematous flat warts on the face may be confused with papular acne vulgaris.

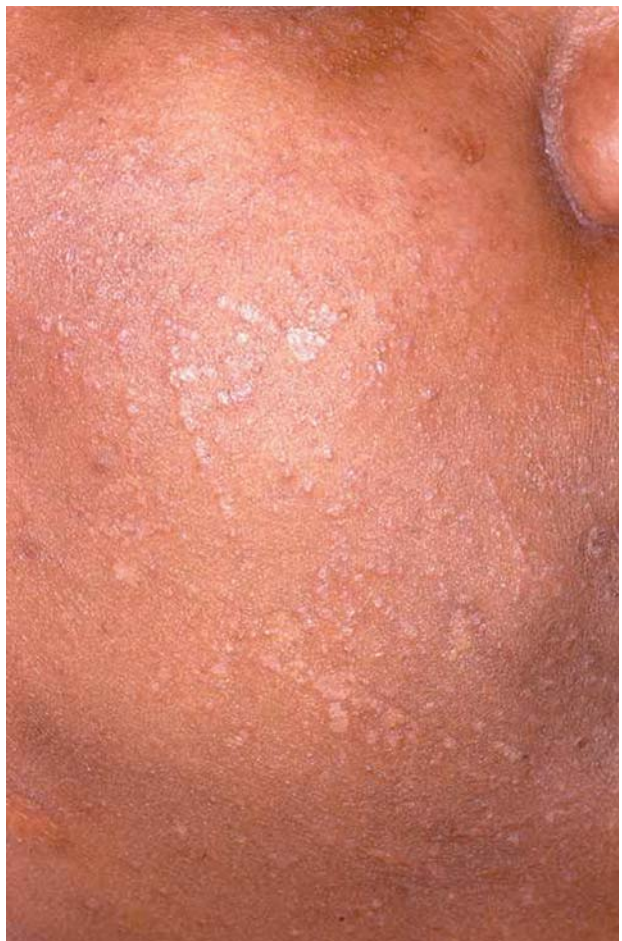
Genital warts occur as exophytic growths affecting the vulva, vagina, cervix, penis, urethra, or perianal region. They present as soft, lobulated, flesh-colored papules or nodules, which may be peduncular or polypoid (Figure 3). The differential diagnosis for genital warts includes condylomata lata of secondary syphilis, which present as wide-based moist papules or nodules. Multiple genital warts may coalesce, forming large cauliflowerlike masses in moist occluded regions such as the perianal skin, vulva, and inguinal creases. In these cases, genital warts must be differentiated from giant condyloma acuminatum (Buschke-Lowenstein tumor), a type of verrucous carcinoma. Genital warts in children may be transmitted by sexual contact, autoinoculation from warts on other areas of the body, vertical transmission perinatally, fomes, or social contact. In children younger than 1 year, vertical transmission is probable. The risk of genital warts as a marker for sexual abuse is higher in children older than 3 years. However, all children with genital warts should undergo a thorough evaluation to rule out sexual transmission and, therefore, sexual abuse.

### Diagnosis

Warts are generally diagnosed clinically; the lesion may be pared with a 15 blade, as described previously, to confirm the diagnosis. In addition, warts can be distinguished by the lack of skin lines crossing their surface. When the diagnosis is unclear or the lesions are refractory to medical treatment, biopsy or surgical removal may be performed. Histologically, common and plantar warts demonstrate papillomatosis, epidermal hyperkeratosis with tiers of parakeratosis, and acanthosis. The rete ridges are elongated and are often bent inward at the periphery, pointing to the center of the lesion. Large vacuolated cells, termed *koilocytes*, in the upper malpighian stratum and granular layer are characteristic. The dermal papillae are elongated and thin with prominent blood vessels. *Verruca plana* demonstrates hyperkeratosis and acanthosis but lacks papillomatosis and parakeratosis. In genital warts, the stratum corneum exhibits only slight thickening, with mucosal lesions showing parakeratosis. The epidermis shows papillomatosis, significant acanthosis, and elongated rete ridges. Mitotic figures are sometimes present. Areas with epithelial cell perinuclear vacuolization in the deeper layers of the malpighian stratum are characteristic.



**Figure 1.** Common wart with smaller satellite lesion on the dorsal aspect of the hand.



**Figure 2.** Numerous flat warts, some in a linear array demonstrating Köbner phenomenon.



**Figure 3.** Multiple coalescing genital warts in a young girl.

### Pathogenesis

Warts are caused by infection with the human papillomavirus (HPV), a double-stranded DNA papovavirus. More than 100 types of HPV have been reported, with each type having a predilection for certain body sites. HPV types are differentiated by the type of epithelium they infect and the malignant potential they exhibit. Common warts are most commonly linked with HPV-2, -4, and -7, plantar warts with HPV-1 and -2, and flat warts with HPV-3 and -10. HPV-6 and -11 have traditionally been associated with condylomata acuminata (anogenital warts), whereas HPV-16, -18, -31, -33, and -35 have been associated with the development of cervical intraepithelial neoplasia and cervical squamous cell carcinoma (Table 1).<sup>4,7</sup>

HPV enters the host through a break in the epidermis, and autoinoculation is common. The precise mechanism by which a cell becomes infected with the virus remains an enigma. Clinically detectable warts emerge a few weeks to 18 months after inoculation; however, in most individuals, the virus is carried without generating any noticeable lesions. The quantity of viral particles in a particular verruca has been correlated with the risk of transmission. Thus, the reduction of infectious virions within a verruca has been shown to decrease the risk of spread to other sites or to others.<sup>4</sup>

### Treatment

Warts typically represent only a minor nuisance; however, they can bleed, itch, hurt, or interrupt

normal functioning. Symptoms are particularly prevalent with plantar warts, which, if located on pressure points, can interfere with ambulation. Although warts may resolve spontaneously, they often persist, with the potential to spread to adjacent or distant sites in the body.<sup>4</sup>

No single specific treatment is indicated for all types of warts, and the many available treatments are less than ideal. Many of the treatments are nonspecific or require multiple visits to the practitioner. Because two thirds of warts will regress spontaneously within 2 years, physicians are often unsure how aggressive therapy should be.<sup>8</sup> Many clinicians are reluctant to treat verrucae at all, especially in children. Unfortunately, it is impossible to predict which wart will involute; therefore, by not treating, a physician may be performing a disservice to the patient. Further, warts can cause significant cosmetic and psychosocial damage in children and adolescents. In addition, because warts may spread to other body sites, there is additional rationale for the initiation of early intervention. Since there is no single effective treatment, the least painful therapy should take priority when dealing with children.

Conventional methods of treatment nonspecifically destroy infected tissue. These methods include cryosurgery; excision; carbon dioxide or pulsed dye laser ablation; and destructive chemical agents such as salicylic acid, cantharidin, podophyllotoxin, and bleomycin sulfate. These treatments generally are well tolerated and effective over time and typically

### Association of Human Papillomavirus (HPV) to Clinical Disease<sup>4-7</sup>

Clinical Disease	HPV Type
Anogenital Lesions	
Condyloma acuminatum	6, 11
Cervical intraepithelial neoplasia	Most frequent: 16, 18, 31, 33, 35 Others: 39, 42–45, 51, 52, 56
Cervical squamous cell carcinoma	Strong association: 16, 18, 31, 33, 35 Moderate association: 39, 45, 51, 52, 56 Weak association: 6, 11, 42–44
Nongenital Lesions	
Common wart	Most frequent: 2, 4, 7 Others: 1, 26, 27, 29, 57, 65, 75–78
Plantar wart	Most frequent: 1, 2 Others: 4, 60, 63
Flat wart	Most frequent: 3, 10 Others: 27, 28, 38, 49

do not result in scarring. However, these procedures are painful, can be intimidating to children, and often require multiple treatments. Newer nondestructive alternatives are available, including modalities that stimulate immunologic responses or provide antiviral activity. Immunomodulating agents used to treat verrucae include cimetidine, imiquimod, retinoids, and contact-sensitizing compounds. A recent addition to the list of antiwart therapies includes cidofovir, an antiviral agent.

Liquid nitrogen cryotherapy is a safe and effective method for treating different varieties of warts in virtually all locations. The physician should apply the liquid nitrogen for 5 to 25 seconds and include a 1- to 2-mm area surrounding the verruca to ensure adequate depth of freezing.<sup>9,10</sup> For hyperkeratotic warts, it is usually beneficial to pare the lesion down prior to cryosurgery because the excess keratin can act as a barrier to treatment. Cure rates of 60% to 80% have been reported.<sup>9,10</sup> Unfortunately, the application of liquid nitrogen can cause some stinging and can frighten children. When performing cryosurgery, it is best to use a cotton-tipped applicator instead of a cryospray gun because the cotton swab is less intimidating. Multiple office visits are often needed. Recent studies comparing the use of cryotherapy and duct tape occlusion to treat warts have shown duct tape to be

of equal or greater efficacy; thus, duct tape should be considered as an alternative or adjunctive treatment for children.<sup>11,12</sup>

Both carbon dioxide and pulsed dye laser treatment also have been used for recalcitrant warts. Because these treatments are painful and expensive and carry the risk of scarring, they should be reserved for cases in which more conservative measures have failed.<sup>13,14</sup>

Salicylic acid, a compound available by prescription or over the counter, is a popular method of treatment because it is inexpensive, can be administered by the patient at home, and results in few complications.<sup>11</sup> In 2000, a systematic review of local treatments for cutaneous warts found salicylic acid to be the most effective agent, with a 75% cure rate compared with a 48% cure rate in controls.<sup>15</sup> Unfortunately, this technique can cause some local irritation, and it requires patient compliance.

Cantharidin is a potent blistering agent obtained from the blister beetle (Spanish fly). When applied to a verruca, it causes the superficial layer of the epidermis containing the wart and HPV virions to swell.<sup>16</sup> A compound containing 1% cantharidin, 30% salicylic acid, and 2% to 5% podophyllum resin, applied for 2 hours and then removed with an alcohol swab, is a very effective treatment that causes little pain upon application.<sup>17</sup>

Painful tense blisters develop 12 to 24 hours after application. The main disadvantage of this treatment modality is that it occasionally results in the development of a ring of satellite warts around the blisters. Also, treatment with cantharidin requires multiple office visits and application by a physician. Because of recent rulings from the US Food and Drug Administration, cantharidin is available only from pharmacies that independently formulate it or from Canada.

Podophyllum resin is a chemotherapeutic agent that has been used as a first-line therapy for condylomata acuminata for over a decade.<sup>2</sup> It is a crude resin of the May apple plant and exerts its cytotoxic effect by interfering with microtubule formation during metaphase. Podophyllum resin does not cause pain when applied, but tenderness often results 6 to 24 hours after treatment and may persist for several days. In addition, podophyllum resin is associated with severe local and systemic side effects and must be applied by a physician. Podofilox, which contains 0.5% podophyllotoxin, has largely replaced podophyllum resin since it can be applied by the patient at home.<sup>18</sup> Efficacy rates of purified podofilox have been reported to be as high as 88% after 3 months of therapy, but a high relapse rate drops cure rates to 30%.<sup>2</sup> Although podofilox has been approved for home treatment, its safety and efficacy have not been studied in children. However, podofilox should be considered for the treatment of symptomatic, persistent anogenital warts in children.<sup>2</sup>

Another chemotherapeutic agent used in the treatment of warts is bleomycin sulfate, a powerful inhibitor of DNA synthesis. Large persistent warts resistant to more traditional therapies can be treated by injection of bleomycin into the verruca with a narrow gauge needle.<sup>19</sup> Cure rates of up to 92% have been reported with this method.<sup>20</sup> However, this therapy can be extremely painful and generally requires a local anesthetic. Although uncommon, Raynaud phenomenon and nail loss or dystrophy have been reported after treatment with intralesional bleomycin.<sup>21,22</sup> Therefore, bleomycin should be employed only by experienced practitioners when more conservative treatments have failed.

In contrast to traditional methods of therapy, immunomodulating agents are less painful and thus more easily tolerated by children. However, their efficacy has yet to be thoroughly demonstrated. One such agent, cimetidine, is a histamine H<sub>2</sub> receptor antagonist that is available over the counter to inhibit gastric acid production. However, in high doses, it is thought to act as an immunomodulatory agent by enhancing the cell-mediated immune

response. In open-label studies, cure rates for cimetidine have reached 82%, but small controlled trials of the agent have failed to demonstrate efficacy superior to that of placebo.<sup>23,24</sup>

Imiquimod, another immune response modifier, confers an antiviral state by inducing interferon alfa. Interferon alfa is the body's natural defense against viral infection. To date, imiquimod has been used primarily in the treatment of genital warts.<sup>25</sup> Efficacy rates differ with site of infection. Penile warts showed 30% resolution on the shaft and 60% clearing under the foreskin, compared with vulvar warts, which showed 80% resolution.<sup>26</sup> Treatment for cutaneous warts has not been as successful.<sup>27</sup> In addition, imiquimod can produce some itching and burning at the site of application.

Topical application of synthetic retinoids such as tretinoin and acitretin also has been used to combat HPV infection.<sup>28</sup> Their greatest success has been in the treatment of flat warts and verrucous keratoses.

The last group of immunomodulators includes the contact-sensitizing agents, which work by generating a type IV allergic reaction. The prototypical contact-sensitizing agent is dinitrochlorobenzene (DNCB). Pooled data from 2 small randomized controlled studies comparing DNCB with placebo showed cure rates of 80% compared with 43%, respectively.<sup>10</sup> However, the use of DNCB has been curtailed in children because of its mutagenic potential.<sup>29</sup> It has largely been replaced with the agents squaric acid dibutylester and diphenycprone (diphenylcyclopropenone). Squaric acid dibutylester has shown efficacy with minimal side effects in the treatment of multiple and resistant warts in children.<sup>30,31</sup> Diphenycprone has been used to treat recalcitrant warts. However, it requires multiple sequential applications, and its use is limited by side effects, including painful local blistering and a dyshidrosisl-like or more generalized eczematous eruption.<sup>32</sup>

The newest addition to the list of possible wart treatments is the antiviral agent cidofovir. Cidofovir is an acyclic nucleoside phosphonate, which has demonstrated antiviral activity against certain DNA viruses, including HPV. Although case reports have recorded the efficacy of compounded 3% cidofovir cream in refractory warts in children, cidofovir remains an investigational drug.<sup>33</sup> Future efforts are likely to focus on developing an antiviral agent that is safe, effective, and specific for HPV.

## Conclusion

Warts are very common and benign yet are troubling growths seen frequently in the pediatric population. Diagnosis is usually made clinically but can be confirmed histologically in challenging cases. Although

most warts will eventually regress spontaneously, practitioners should offer treatment to patients who are distressed by the lesions. A variety of treatments are available, and the choice of treatment method should be individualized according to each patient's particular clinical presentation and preferences.

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