Pediatric Warts: Update on Interventions

Nanette B. Silverberg, MD

PRACTICE **POINTS**

- Warts are caused by infection with the human papillomavirus.
- Warts are extremely common in all age groups, but risk factors and types of lesions vary by age and location of lesions.
- Therapies for pediatric warts are characterized according to 6 major categories: destructive; immune stimulating; immune modulating, including normalization of epithelial growth; vascular destructive; irritant; and nitric oxide releasing.

Warts are superficial viral infections of the skin that are extremely common in children. The infection usually lasts more than 1 year and can be moderately contagious in specific settings; for instance, warts are particularly common and spread more easily in the setting of atopic dermatitis, a chronic, itchy pediatric skin condition caused by barrier and immune defects. Therapies for pediatric warts are characterized according to 6 major categories: destructive; immune stimulating; immune modulating, including normalization of epithelial growth; vascular destructive; irritant; and nitric oxide releasing. The standard of care is the use of destructive therapies, with immune-stimulating and vascular destructive therapies reserved for more prolonged, extensive, or treatment-resistant infections. In this article, a successful paradigm for management of pediatric warts is provided, with enhanced outcomes based on further insight into the disease course and patient selection.

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The definition of warts is variable, largely reflecting their manifold appearance, biologic potential, and public health concerns. One vernacular dictionary defines warts as:

> Small, benign growths caused by a vital infection of the skin or mucous membrane. The virus infects the surface layer. The viruses that cause warts are members of the human papilloma virus (HPV) family. Warts are not cancerous but some strains of HPV, usually not associated with warts, have been linked with cancer formation. Warts are contagious from person to person and from one area of the body to another on the same person.[1]

The World Health Organization defines warts by their structural components as:

> Human papillomavirus (HPV) is a small, nonenveloped deoxyribonucleic acid (DNA) virus that infects skin or mucosal cells. The circular, double-stranded viral genome is approximately 8-kb in length. The genome encodes for 6 early proteins responsible for virus replication and 2 late proteins, L1 and L2, which are the viral structural proteins.[2]

In pediatric and adolescent dermatology, warts often are defined by their location and morphology; for example, facial warts typically are flat, minimally hyperkeratotic, or filiform, wherein the base is narrow and the lesion is tall, growing at a 90° angle to the surface of the skin. On the arms and legs, warts usually present as round to oval papules with overlying thick hyperkeratosis and/or callosity.[3,4] Common warts usually are flesh colored or lighter, and heavily pigmented lesions should be evaluated dermoscopically for a pigment network and biopsied when pigment is present.[5]

In this article, a successful paradigm for management of pediatric warts is provided with enhanced outcomes based on further insight into the disease course and patient selection.

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Epidemiology of Pediatric Warts

There are more than 200 types of human papillomaviruses (HPV), with more than 100 oncogenic types. There is quite a bit of homology by species and genus that contributes to cross-immunity and similar behavior between certain types of HPV. The lifetime incidence of warts is very high. Approximately 30% of children develop a wart.[6] A review of the 2007 National Health Interview Survey of 9417 children demonstrated a steady increase in prevalence of warts from 1 to 2 years of age to 7 to 8 years of age, with a peak at 9 to 10 years of age and a plateau at 11 to 17 years of age. Warts were most common in non-Hispanic white children and less common in black children.[7] In an in-person survey of 12,370 individuals aged 18 to 74 years from 5 European countries, warts were the most common physician-diagnosed (27.3%) and self-reported (41.0%) dermatologic condition. Warts are more common in Northern countries (eg, Netherlands, Germany).[8] Children with atopic dermatitis have a higher risk of developing warts and extracutaneous infections. In one study, children with warts and atopic dermatitis had a higher number of infections and food allergies and higher incidence of asthma and hay fever than either condition alone.[9]

Clinical Presentation of Warts

Warts usually present as common, palmoplantar, flat, or filiform in childhood, but variations by age are common (eFigure). The common and palmoplantar variants often are caused by HPV types 1 and 2.[4,5] In infancy, vertically transmitted HPV infections can cause juvenile-onset respiratory papillomatosis or vertically transmitted condyloma. Juvenile-onset respiratory papillomatosis refers to upper respiratory papillomas that are difficult to eliminate and has been associated with exfoliated cervical cell testing with 18.1% (13/72) typed HPV-positive, which allows neonates to be exposed to HPV in the upper respiratory tract in utero.[10]

Vertically transmitted condyloma is a difficult topic. Much data supports the vertical transmission of condyloma as the leading cause of condyloma in small children; however, a reasonable amount of caution is needed in this patient population. In cases suspicious for sexual abuse as well as those presenting in children 4 years and older, formal household evaluation by a sexual abuse clinic and mandatory reporting is needed. Anywhere from 2.6% to 32% of cases of genital warts in children have been reported to be caused by sexual abuse.[11-13] Therefore, most investigators have recommended careful review of the patient's history and socioeconomic circumstances as well as a thorough physical examination. Mandatory reporting of suspected child sexual abuse is required in suspicious cases. Because HPV type 16 has been found in vertically transmitted cases, concern for long-term oncogenesis exists.[11-13]

Adolescents generally present with lesions on the hands and feet. Plantar warts often are caused by HPV types from the alpha genus. Subtypes noted in plantar warts include HPV types 1a, 2, 27, 57, and 65.[14] By 15 years of age, genital HPV becomes a common adolescent infection, persisting into adulthood.[15] When studied, genital HPV often is subclinical or latent and often is preventable through vaccination. High-risk oncogenic alpha-genus HPV types can immortalize human keratinocytes. When HPV types 11, 16, 18, and 31 are compared, HPV-18 has the highest oncogenic potential based on colony-stimulating potential.[16] Vaccination with the 9-valent HPV vaccine is recommended in adolescence due to the concern for exposures to both low-potential (HPV types 6 and 11) and high-potential (HPV types 16 and 18) oncogenic HPV types. Data strongly support the benefit of 9-valent HPV vaccination in the prevention of sexually transmitted HPV in both males and females.[17]

Contagion of HPV is easy due to its excellent survival of fomites on surfaces, which generally is how warts are transferred in gym or pool settings where individuals who walk barefoot in changing rooms are almost twice as likely to contract plantar warts (odds ratio, 1.97 [95% CI, 1.39%-2.79%]).[18] In another case series, walking barefoot, using a swimming pool, and having a household contact with warts were the leading risk factors for contraction of warts in children younger than 13 years.[19] Children often transfer warts from site to site as well as to siblings and other close contacts. Skin-to-skin contact is responsible for sexual transmission of warts, and surface transmission occurs via fomites. Entry of the virus often occurs through small breaks in the skin. Other modes of transmission include orogenital.[20]

Therapeutic Options

Although the nuances of each available treatment for pediatric warts are beyond the scope of this article, the main core of therapy is 1 of 3 approaches: (1) observation, (2) over-the-counter salicylic acid therapy, and (3) in-office cryotherapy. Observation is an affirmed style of therapy for warts, as it is expected that two-thirds of warts will spontaneously resolve in 2 years and three-quarters will resolve in 3 years.[4,5] Condyloma in children has been responsive to therapies such as cryotherapy and imiquimod,[13] but spontaneous clearance in 5 years has been noted in 76% of children,[21] which is linked to development of spontaneous immune response in most individuals.

Therapies for pediatric warts are characterized according to 6 major categories: destructive; immune stimulating; immune modulating, including normalization of epithelial growth; irritant; vascular destructive; and nitric oxide releasing (eTable).

Destructive Therapies—Destructive therapies for warts often are implemented in cases of disfigurement, discomfort/pain, and/or spreading, as well as to control contagion. According to a 2001 Cochrane review, salicylic acid has the best evidence of all therapeutics for the clearance of warts compared to placebo.[24] On the other hand, aggressive cryotherapy and combined salicylic acid

and cryotherapy had the best evidence in their favor in a 2011 meta-analysis by Kwok et al.[25] Both salicylic acid and cryotherapy are considered destructive therapies. A recent meta-analysis of cantharidin, another destructive therapy, showed that local cantharidin alone as well as in combination with salicylic acid and podophyllotoxin showed good efficacy for warts; however, increased caution should be exerted with the combination regimen in young children due to a potential increase in the side-effect profile (eg, severe blistering).[22] Other destructive agents such as topical retinoids can only peel surface layers of the skin and therefore are limited to flat facial warts, which are not expected to have an extensive hyperkeratotic layer; however, with occlusion, agents such as adapalene gel 0.1% can be used even on plantar warts with some efficacy.[29]

Immune-Stimulating Therapies—Immune stimulants often are used to treat warts in children and adolescents who have many lesions, a prolonged disease course, disfigurement, and/or subungual localizations, as well as in those who have been treated with multiple destructive methods without success. Topical imiquimod and oral cimetidine are readily available, while squaric acid (at-home or in-office therapy) and intralesional candida antigen can be used in offices that carry these agents. Topical imiquimod has been reported to achieve success in genital warts in children,[13] with good efficacy in recalcitrant, periungual, and subungual warts when used for up to 16 weeks.[31] In one randomized clinical trial, imiquimod cream 5% combined with salicylic acid 15% was applied to warts for 6 to 10 hours for 5 consecutive days per week versus cryotherapy with liquid nitrogen every 2 weeks for a maximum of 3 months. At the end of the study period, 81.1% (30/37) of participants treated with imiquimod and salicylic acid showed clearance of their warts versus 67.3% (33/49) of those treated with cryotherapy.[32]

Oral cimetidine has been reported to be successful in treating recalcitrant warts in more than 80% of children when dosed at 30 to 40 mg/kg 3 times daily, requiring 6 to 12 weeks to achieve clearance. Side effects of oral cimetidine include many cytochrome P450 interactions; gynecomastia, which limits usage in teenaged males; and stomach upset.[30]

Treatment of recalcitrant pediatric warts with intralesional candida antigen has been associated with side effects consistent with delayed-type hypersensitivity reactions. Injections should be administered once monthly, with a minimum of 3 cycles if not effective and up to 6 cycles where partial efficacy is noted. In a retrospective review of 220 cases, 70.9% of children showed complete clearance and 16.8% had partial response.[33] However, the treatment may be limited in children by fear of needles.

Squaric acid dibutyl ester is a universal allergen that is not mutagenic on Ames testing and causes milder allergy symptoms than the mutagenic dinitrochlorobenzene and less erythema and pruritus than diphencyclopropenone. Squaric acid dibutyl ester home therapy was evaluated in 61 children with at least one nonfacial wart.[34] Application began with squaric acid dibutyl ester in acetone (SADBE) 2% sensitization on the arm followed by at-home application of SADBE 0.2% three to seven times weekly for a minimum of 2 months to determine benefit and for 3 to 4 months as needed; however, average response was 7 weeks. The average complete clearance was 58% and partial clearance was 18%. Side effects included erythema and mild itching as well as urticaria in one case.[34] In-office SADBE also has been evaluated in children. In a case series that included 29 children sensitized with SADBE 1% to 2% under occlusion followed by once monthly application of SADBE 0.5% to 5.0% to their warts, 69% clearance and 10% partial clearance was noted after a little more than 4 months of treatment.[35] One retrospective review compared combination SADBE, trichloroacetic acid (TCA), and cantharidin both alone and in combination as duos (eg, SADBE and TCA) or trios (SADBE, TCA, and cantharidin).[23] Of the 74 children whose medical charts were reviewed, the addition of pretreatment of warts with TCA 50% prior to in-office sensitization and monthly in-office application of SADBE increased treatment response to 100% with an average 2.45 months of therapy, whereas no enhancement was noted with cantharidin. Therefore, it appears that there may be enhanced immune reactivity when TCA pretreatment of warts is performed.[23]

Immune-Modulating Therapies (Including Normalization of Epithelial Growth)—The most novel immunologic therapy for warts is plerixafor, an agent used to treat WHIM (warts, hypogammaglobulinemia, infections, and myelokathexis) syndrome, which has been linked to heterozygous gain of function mutations in the chemokine receptor CXCR4 (located on 2q22). In WHIM syndrome, the mutated CXCR4 is more sensitive to CXCL12 activation. Plerixafor is a selective reversible antagonist that blocks the capacity of the chemokine CXCL12 to sustain the permanent activation of CXCR4.[37] Combination therapy with plerixafor and topical imiquimod has resulted in wart improvement in WHIM syndrome patients in a small series.[38]

Oral isotretinoin has been described to be efficacious over placebo at a dosage of 30 mg daily for 12 weeks and can be used in teenagers but requires standard monitoring.[36]

Irritant Therapies—Duct tape is a classic agent that produces maceration and irritation of warts. Application of duct tape over warts has been described in cycles of 6 days on, 1 day off with weekly repetition for a few months but usually not on the palms or soles due to difficulty maintaining occlusive tape in these locations over an extended period of time. In one trial, 85% (22/26) of duct tape–treated cases cleared versus 60% (15/25) of cryotherapy-treated cases over a 2-month maximum therapeutic period.[39]

Vascular Destructive Therapies—The pulsed dye laser is a classic modality that induces localized destruction of blood supply to warts in children. A case series of 61 children treated with the pulsed dye laser revealed 75% overall clearance in an average of 3.1 sessions.

Therapeutic Ladder for Warts in Children

Rung 1: Diagnose the wart(s)
Rung 2: Manage warts in special locations (eg, genital warts require investigation to identify sexual abuse cases as well as the source of transmission; facial warts are associated with a greater risk of scarring and therefore therapies such as topical agents may be used)
Rung 3: Assess the need for therapy, asking "Will the child benefit?"
Rung 4: Use destructive therapies to treat nonfacial lesions, avoiding painful procedures in small children where possible
Rung 5: Use immune-stimulating therapies, reviewing options with caregivers including length of treatment and possible side effects to best choose an intervention
Rung 6: Use garlic or duct tape in patients whose caregivers prefer natural or milder agents
Rung 7: Reserve injections and laser therapy for cases with few recalcitrant lesions

The usage of this therapy often is limited to institutions where the technology is readily available for usage.[40]

Nitric Oxide–Releasing Therapies—Nitric oxide release may increase local blood flow, thereby increasing immune response, or may have a primary mechanism of antimicrobial activity, which is why these agents have been investigated for wart treatment. Topical garlic has been described anecdotally as a therapy for thin childhood warts with the putative mechanism being nitric oxide release.[42] A new investigational drug recently has had phase 2 data published. Berdazimer sodium plus carboxymethyl cellulose hydrogel has demonstrated benefit in adult warts, but data in children is lacking.[41]

Therapeutic Ladder for Childhood Warts

The therapeutic ladder (Table) for childhood warts starts with first doing no harm. Although many parents are disturbed by their child's condition, the natural history of resolution is spontaneous and therefore no therapy is required in many cases. The child and his/her caregivers should be engaged to determine if he/she is emotionally disturbed or uncomfortable with their lesions and to address any fears and concerns that some children may experience (eg, contagion risk, pain with ambulation, ostracism). For example, children with hand warts may report that other children will not hold their hand while in line at school. Prominent facial lesions can be particularly problematic for children due to teasing and bullying.

Conclusion

Warts are a common infection in childhood caused by the ubiquitous HPV virus. Therapeutic options abound, but most cases are either ignored or treated with over-the-counter salicylic acid or in-office cryotherapy. The decision to employ alternative therapeutic options requires agreement by the child, his/her caregiver, and the treating physician and can be tailored to suit the desires and needs of the child. Whether or not therapy is offered, spontaneous clearance is frequently seen in common warts. On the other hand, genital warts are associated with later conversion to malignancies of the genital tract; therefore, encouragement of HPV vaccination is needed in the adolescent population to best ensure long-term genital health.

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eTABLE. Select Therapeutic Options for Pediatric Warts

Treatment	Patient Selection	Therapeutic Regimen	Expected Resolution Rate	Side Effects
Destructive				
Cantharidin[22]	For toddlers and school-aged children and pain-intolerant patients who have not had success with salicylic acid therapy	Apply sparingly to lesion and surrounding skin; repeat every few weeks as needed	81%–100% with combined agents	Pain, blistering, hypopigmentation, hyperpigmentation, ring warts[22,23]
Cryotherapy[24,25]	Children with a limited number of lesions and adolescents; use sparingly on facial lesions (eg, apply with a cotton swab)	Apply once every 2–3 wk	Complete clearance in 57% (n=97) after 3 sessions[26]	Pain, blistering, hypopigmentation, or rarely nerve or nail damage[27]
Salicylic acid[24]	Children >2 y with nonfacial warts; avoid use on the digits in patients who are known to suck the digits	Apply 1–2 times daily	6–12 wk	Allergic skin reactions (eg, contact dermatitis or systemic hypersensitivity), rash, dryness, scaling, irritation, itching, swelling, burning sensation, redness, excessive skin growth, discoloration of the skin, blistering, pain, and hypersensitivity at application site[28]
Topical retinoids[29]	Facial flat warts sparing the eyelids	Apply sparingly to facial lesions, avoiding the eyelids; apply under occlusion for soles of the feet	NA	Peeling, erythema, irritation
Immune stimulating				
Cimetidine[30]	Extensive warts including subungual, periungual, and other types unable to be treated with localized destruction	30–40 mg/kg divided 2 or 3 times daily for 6–12 wk	Complete clearance in 81% (26/32) by 2 mo of therapy[30]	Stomach upset, gynecomastia, high rate of interactions with other medications involving cytochrome P450 metabolism[30]
Imiquimod[31,32]	Recalcitrant periungual and subungual warts	Apply 5 nights weekly, can be combined with salicylic acid	Up to 80% clearance after 16 weeks[31]	Irritation, redness, ulceration, flulike symptoms, rarely vitiligo lesions
Intralesional candida antigen[33]	Solitary recalcitrant warts	3 intralesional injections of standardized volume (usually 0.1–0.2 mL) administered once every 3 wk for a total of 3 sessions[33]	70.9% complete and 16.8% partial clearance after 3 sessions (N=220)[33]	Erythema, digital swelling, pain, tenderness
Squaric acid dibutyl ester home therapy[34]	Recalcitrant nonfacial periungual or subungual warts	Squaric acid 2% sensitization 10 d prior to treatment, then 0.2% SADBE applied at home 3–7 times per wk	58% complete and 18% partial clearance (N=61), usually 6–7 wk[34]	Erythema, itching, dermatitis, urticaria

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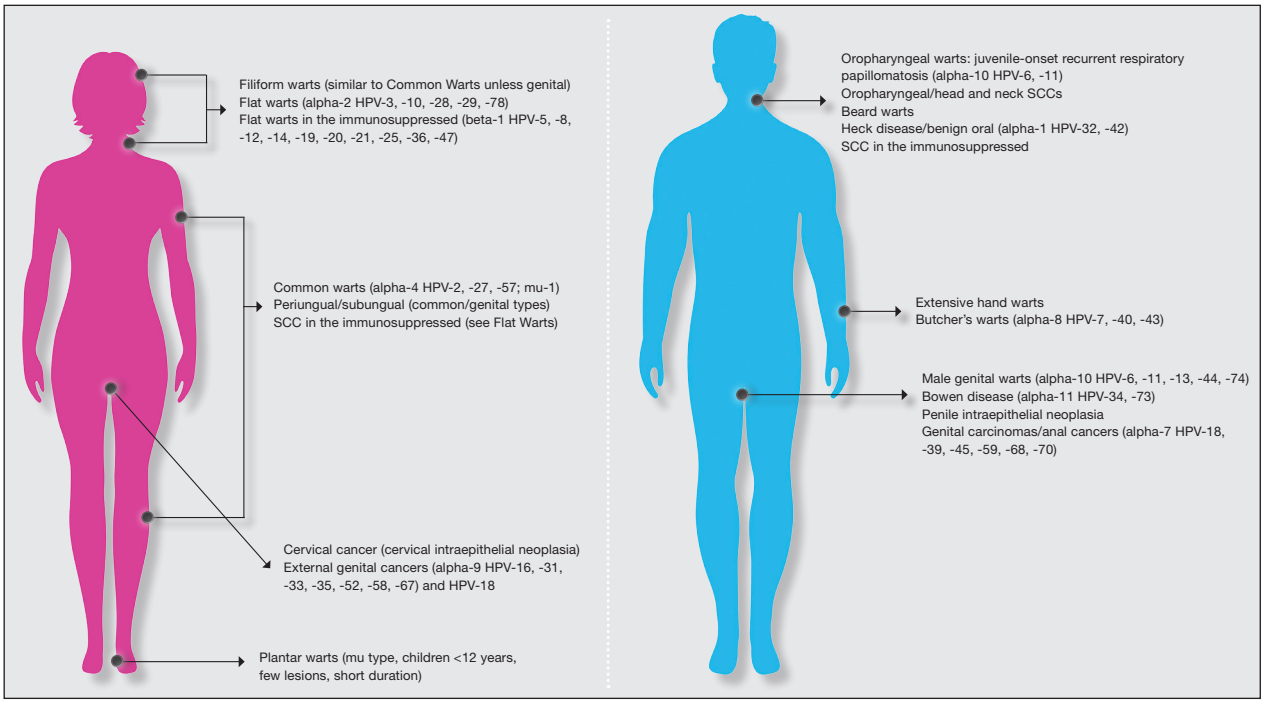
eTABLE. (continued)

Treatment	Patient Selection	Therapeutic Regimen	Expected Resolution Rate	Side Effects
Immune stimulating (continued)				
Squaric acid dibutyl ester in-office therapy[35]	Recalcitrant nonfacial periungual or subungual warts	Squaric acid 1%–2% sensitization under occlusion followed by in-office application of squaric acid 0.5%–5.0% every 2–4 wk[35]; can be enhanced by applying TCA before application on wart sites (nonfacial)[23]	69% clearance and 10% partial clearance (N=29)	Itching, burning, redness, swelling, hives
Immune modulating (including normalization of epithelial growth)				
Isotretinoin[36]	Patients with extensive flat facial warts who can swallow a pill and follow pregnancy prevention and laboratory plan	30 mg once daily for 12 wk[36]	16 patients in the treatment group vs 15 patients in the placebo group showed clearance[36]	Teratogenicity; cheilitis; pruritus; dry skin; dry eyes; rash; muscle pain; headache; diffuse alopecia; photosensitivity; impaired vision; elevated cholesterol, triglyceride, AST (SGOT), ALT (SGPT), and/or bilirubin levels; altered white blood cell or platelet counts[36]
Plerixafor[37,38]	WHIM syndrome	1.2 mL=24 mg various administration regimens have been described (consult immunology and hematology)	Beneficial for warts in WHIM syndrome patients when combined with imiquimod 5%[37,38]	Refer to package insert
Irritant therapy				
Duct tape	Warts not on the face, hands, or feet	Weekly replacement of duct tape over the wart site	85% clearance after 2 mo in a head-to-head comparison with cryotherapy[39]	Maceration, irritation, pain with removal
Vascular destructive				
Pulsed dye laser	All cutaneous warts	Once monthly	75% (46/61) showed total clearance after an average of 3.1 sessions[40]	Scarring, pain, discoloration
Nitric oxide releasing				
Topical garlic, berdazimer	Warts in small children and individuals desiring natural therapeutics	Various regimens	NA	Not well defined

Abbreviations: NA, not available; SADBE, squaric acid dibutyl ester in acetone; TCA, trichloroacetic acid; AST, aspartate aminotransferase; SGOT, serum glutamic-oxaloacetic transaminase; ALT, alanine aminotransferase; SGPT, serum glutamic-pyruvic transaminase; WHIM, warts, hypogammaglobulinemia, infections, and myelokathexis.



eFIGURE. Warts by types and locations. HPV indicates human papillomavirus; SCC, squamous cell carcinoma.