Epidemiology and Pathogenesis of Warts in Children

Clinical Diagnosis of Common Warts

Indications for Referral

Treatment Options for Common Warts

Treatment in the Dermatologist’s Office

FACULTY

Bari B. Cunningham, MD
Assistant Clinical Professor of Pediatrics and Medicine (Dermatology)
University of California at San Diego
Director, Dermatologic Surgery
Children’s Hospital and Health Center
San Diego, Calif.

Nanette B. Silverberg, MD
Director, Pediatric Dermatology
St. Luke’s-Roosevelt Hospital Center
New York, NY
Assistant Clinical Professor of Dermatology
Columbia College of Physicians and Surgeons
New York, NY
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Assistant Clinical Professor of Pediatrics and Medicine (Dermatology)
University of California at San Diego
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Director, Pediatric Dermatology
St. Luke’s-Roosevelt Hospital Center
New York, NY
Assistant Clinical Professor of Dermatology
Columbia College of Physicians and Surgeons
New York, NY

Accreditation

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Estimated time to complete this educational activity: 1 hour.

Target Audience

This activity is developed for pediatricians, family physicians, and other health care professionals involved in the diagnosis, treatment, and long-term management of children with warts.

Educational Needs

Warts are caused by various subtypes of the human papillomavirus (HPV) that may occur anywhere on the body. Common warts (verruca vulgaris) typically present on the hands, feet, elbows, knees, and face. Condylomata acuminata (genital warts) may occur on the genitals and in the general diaper area, and may—but do not necessarily—indicate the presence of sexual abuse. A small number of the HPV subtypes have malignant potential, especially in immunocompromised children. Although warts resolve spontaneously in up to two thirds of cases, many patients and their parents prefer to have treatment rather than wait for possible spontaneous resolution. Pediatricians and family physicians need up-to-date information on the relatively painless topical treatments available for wart removal in children that are appropriate for the primary care office. Because up to one third of treated warts resist therapy, primary care physicians also need to be aware of the range of options that may be used by dermatologists to whom they refer patients when topical therapies fail, or when the characteristics of a wart indicate that a biopsy may be necessary.

Learning Objectives

By reading and studying this supplement, participants should be able to:

• Summarize the modalities currently available for the treatment of warts in children, and list the advantages and disadvantages of each.

• Describe the steps that can be taken to minimize pain when treating children for warts.

• List the indications for referring a child with warts to a dermatology specialist.

Faculty and Unapproved Use Disclosures

Faculty/authors must disclose any significant financial interest or relationship with proprietary entities that may have a direct relationship to the subject matter. They must also disclose any discussion of investigational or unapproved uses of products.

Dr Cunningham has received funding from Valeant Pharmaceuticals International. She discusses the unlabeled use of 5% 5-fluorouracil (5% 5-FU) for warts as well as other unlabeled alternatives including cantharidin, squaric acid, and diphenyclopropenone. Dr Silverberg has received funding from Ferndale Laboratories, Inc. She discusses the unlabeled use of 5% 5-FU, imiquimod, liquid nitrogen, duct tape, pulsed-dye laser, and carbon dioxide laser as wart therapy in children. She also discusses the investigational use of 5% 5-FU for wart therapy in children.
Management of Warts in Pediatric Patients

Bari B. Cunningham, MD, and Nanette B. Silverberg, MD

Pediatricians and family physicians are on the medical front line for managing warts in children, with these lesions accounting for a significant number of primary care office visits. Warts are among the most common skin diseases seen by pediatric dermatologists, but specialists see only the 25% of cases that are treatment-resistant.1

Before consulting a physician, most parents attempt to treat warts themselves with home remedies and over-the-counter preparations. Both parents and children are frustrated when these treatments fail, and by the time a physician is consulted, the expectation for a rapid and effective cure is high.

Numerous treatment options for warts are available, but no single method is universally effective. Often, more than one round of monotherapy is necessary; if monotherapy fails, combination therapy may be effective, but usually requires several office visits, further increasing frustration on the part of children and their parents. For this reason, patients and their parents must be educated about the inherently recalcitrant nature of warts, and should be reassured that the appropriate measures are being taken to eliminate the lesions using methods that are least likely to cause discomfort and long-term cosmetic sequelae.

Epidemiology and Pathogenesis of Warts in Children

An estimated 10% to 22% of children develop warts,1 with the incidence peaking during adolescence.2 Warts in children fall into two general categories: those occurring on the genitals and diaper region in infants and toddlers, and those affecting the face, hands, feet, elbows, and knees of children of all ages.

Both common and genital warts result from infection with human papillomavirus (HPV), a coiled, double-stranded DNA virus that infects host squamous cells, causing abnormal cellular replication. More than 90 genotypes of HPV have been identified, but only relatively few HPV types cause warts in children (Table 1). Infection occurs when HPV enters the host’s basal or proliferative cells through surface skin abrasions. A lengthy latency period may occur between infection and the development of clinical lesions. HPV is a relatively hardy virus, which is resistant to destruction.

Warts on the genitals and in the diaper region can be acquired by vertical transmission at birth by a mother with HPV infection of the cervix and/or genitals. The warts that spread to a baby during birth are often either HPV-6 or HPV-11 genotype. Less commonly, the oncogenic genotypes may be vertically transmitted. Rarely, oncogenic genotypes have been linked to cases of early squamous cell carcinoma (SCC) on the genitals in toddlers.3 Warts also may be spread from the caretaker’s hands during diaper changing and in this situation are most commonly due to HPV-2. These warts can be found anywhere within the diaper zone, including the inner thigh and the perianal region.

Genital warts that develop in a child older than 3 years of age may be a red flag for sexual abuse. Some of the types of HPV that are associated with genital warts in sexually abused children have malignant potential; among these are the HPV-16, HPV-18, HPV-31, and HPV-33 genotypes.4 The hands, feet, elbows, knees, and face are the most frequent sites for common warts in children. These warts are usually caused by infection with HPV-2 and HPV-1, neither of which is oncogenic. It is common for a child to spread warts from one part of the body to another via autoinoculation.

Clinical Diagnosis of Common Warts

Most pediatricians and family physicians have no difficulty in identifying childhood warts, which are diagnosed clinically in almost

| Table 1. Types of Warts: Virus and Clinical Correlates |
|-----------------------|----------------|
| Morphology            | Associated HPV Viruses |
| Common warts          | 1-4, 7, 10           |
| Mosaic warts          | 1-4, 7, 10           |
| Callous-like warts    | 1-4, 7, 10           |
| Filiform warts        | 1-4, 7, 10           |
| Flat warts (tinea versicolor-like) | 3, 5*, 8*, 10, 12, 14, 15, 17, 25-30, 41 |
| Donut warts           | Various†             |
| Subclinical infection | Various              |

*These HPV types are associated with immunosuppression and skin cancer formations;
†Associated with prior therapy of warts
HPV = human papillomavirus

Source: Nanette B. Silverberg, MD.
all cases. The lesions have a characteristic flesh color and tend to occur on sites subject to trauma, as noted above. However, warts can spread anywhere, and an examination of a child who presents with warts should include careful inspection of the whole body, including the periungual areas, perioral skin, and the plantar aspects of the feet (plantar warts). Plantar warts may be readily identified by their typically flattened appearance (caused by pressure from standing) and by the cornified epithelium that surrounds them.

Warts can be exquisitely tender, and have a tendency for pinpoint bleeding when their surface is pared away. It is this latter feature that distinguishes warts from calluses, corns, actinic keratoses, nevi, or acrochordons.

Flat warts (verruca plana) are smooth with flat tops and can have a yellow-brown color. They tend to appear on the face and along scratch marks (Koebner phenomenon). Flat warts commonly are spread by autoinoculation.

**Indications for Referral**

A wart’s location, appearance, and history can guide the decision about referring a patient to a dermatologist. Any patient with a pigmented wart should always be referred for a biopsy to rule out verrucous pigmented melanoma. Other lesions (or wartlike lesions) that warrant referral to a dermatologist for biopsy include those that spread despite treatment, as well as those that enlarge and/or ulcerate. In such cases, SCC must be ruled out.

Warts in immunocompromised children may need to be biopsied as well. Children who are infected with human immunodeficiency virus, who are undergoing cancer chemotherapy, those who have received an organ transplant, and/or children who are on immunosuppressive therapy are susceptible to oncogenic strains of HPV.

**Treatment Options for Common Warts**

The same modalities that are used to treat warts in adults can be used in pediatric patients, but the approach to younger patients poses some unique challenges. While most adults and many older children and teenagers are willing to tolerate some discomfort in the treatment of their warts, younger children may not be as willing to cooperate. Fortunately, with the range of treatment options available, avoidance of pain is often possible. Just as important as patient comfort is attention to the long-term cosmetic consequences of treatment. Therapy that is least likely to produce scarring should always be the first choice, particularly when treating warts on the face.

One option is to simply observe the lesions, because the majority of common warts resolve spontaneously within 2 to 3 years. In their seminal study on warts, Massing and Epstein5 reported that 30% will clear in 6 months; another 36% will resolve over the course of the next 18 months, and 9% clear in the following year.

The American Academy of Dermatology lists the indications for the treatment of warts, including the patient’s wishes (Table 2). Children may be more interested than their parents in having their warts removed, frequently citing negative comments from other children as a reason for seeking treatment. The number and location of the warts as well as the age of the child all guide treatment choices for management of common warts.

The most commonly used treatments for warts are summarized in Table 3. Few of these treatments have US Food and Drug Administration (FDA) approval for this indication; nonetheless, they continue to be widely used and studied.

The most commonly used treatments for warts in children involve either immediate wart destruction with liquid nitrogen or electrodessi-
cation, or their more gradual destruction with a topical medication such as 5% 5-fluorouracil (5% 5-FU) or the immune response modifier imiquimod. It may be necessary to use combinations of these therapies or to consider other alternatives to achieve clearance of warts. To date, neither 5% 5-FU nor imiquimod has been approved by the FDA for the treatment of common warts. Imiquimod is approved for the treatment of genital warts in patients as young as 12 years of age as well as actinic keratoses. When using cryosurgery or topical treatments, it is helpful to pare the hyperkeratotic surface of warts first; this relieves pressure and enhances penetration of the medication.

Cryosurgery

Liquid nitrogen has been the gold standard of wart therapy for almost 30 years. The usual approach involves application of a 20-second burst of liquid nitrogen to each wart every 2 to 3 weeks until the lesions are destroyed. In their classic study on this treatment, Bunney and colleagues noted that efficacy drops significantly when the interval between treatments exceeds 3 weeks. In addition to paring, as noted, the efficacy of cryosurgery for thick warts can be enhanced by pretreatment with 5% 5-FU, imiquimod, or salicylic acid.

Cryosurgery should be utilized with caution in children with facial warts because of the risk for hypopigmentation and scarring; the risk for scarring is greater on the face than elsewhere on the body. Another disadvantage of cryosurgery in the pediatric population is that it is painful. Moreover, the use of liquid nitrogen may induce blisters, and, when performed over the digital nervous and vascular bundle, may cause nerve and vascular damage. Patients with bleeding diatheses are not candidates for cryosurgery because of their risk for severe hemorrhagic bullae.

5% 5-Fluorouracil

Topical 5% 5-FU cream may be used for both common and genital warts; it is safe to use on the face and poses minimal risk of scarring. The mechanism of action of this pyrimidine metabolite is related to its interference with DNA and RNA synthesis, which disrupts viral replication and epidermal cell turnover.

Topical 5% 5-FU is applied locally once-daily by the parents at home. The cure rate has been estimated to be approximately 50%, comparable in some studies to that seen with salicylic acid.

The effectiveness and safety of 5% 5-FU is currently being evaluated in a study of 39 children between 4 and 18 years of age, comparing once-daily or twice-daily applications of 5-FU with nightly duct tape occlusion for 6 weeks. The protocol required that the warts be pared prior to application of the medication.

To be eligible for enrollment in this study, patients were required to be in good health and to have at least two warts on the hands or fingers, but not on the periungual region. Excluded from the study were patients who were immunocompromised or who had significant medical problems, those who had used any oral or topical medication for 14 days prior to entry into the study, or those who were pregnant. In addition, children who were current thumbsuckers and patients who had warts larger than 3 cm in diameter were not eligible for this study.

A total of 140 warts were treated. Thirteen patients had warts that had been resistant to at least 1 year of prior therapy.

To assess the risk for systemic toxicity, complete blood counts and 5-FU levels were obtained for each patient at baseline and after 6 weeks of treatment. Efficacy was assessed on the basis of improvement in thickness and improvement in hyperkeratosis. In addition to physician assessments of safety and efficacy, patients and parents were asked about their perceptions of improvement and about their satisfaction with the overall ease and comfort of the treatment.

The study has been completed and the results have been analyzed. The data have been submitted for publication elsewhere, but it can be noted here that significant improvements were seen, that therapy was well-tolerated, and that no serious side effects were seen. Follow-up assessments will be performed at 3 and 6 months to check for recurrence of warts.

When prescribing topical 5% 5-FU, physicians should counsel parents that this agent often produces irritation.

Application of 5% 5-FU to the periungual region should be avoided because the medication can interfere with growth of the nail, leading to a chemical onycholysis. It should not be used in children who suck their thumbs or in widespread warts due to the increased potential for systemic absorption.
Management of Warts in Pediatric Patients

Imiquimod

Much of the data on use of imiquimod to treat common warts in children come from small case series and case reports. These data suggest that imiquimod may be an effective topical therapy in children for the treatment of recalcitrant subungual and periangual lesions. In one study by Hengge and colleagues, daily application of imiquimod to warts for 5 days out of 7 for 16 weeks resulted in a 30% clearance rate. In clinical settings, the therapeutic response may be more variable when imiquimod is used as monotherapy. Combination therapy with liquid nitrogen may increase efficacy.

Side effects with imiquimod are usually limited to mild, transient erythema and pruritus, but erosions, ulcerations, and secondary bacterial infections also have been reported with use of this agent. Imiquimod poses little risk of scarring when used to treat facial warts.

Occlusion With Duct Tape

The application of duct tape to a wart is a treatment option that is particularly attractive for use in children because it is painless, inexpensive, and carries no risk for toxicity. However, the effectiveness of duct tape monotherapy has not been definitively established. In the study published in 2002 by Focht and colleagues, daily application of imiquimod to warts for 5 days out of 7 for 16 weeks resulted in a 30% clearance rate. In clinical settings, the therapeutic response may be more variable when imiquimod is used as monotherapy. Combination therapy with liquid nitrogen may increase efficacy.

Side effects with imiquimod are usually limited to mild, transient erythema and pruritus, but erosions, ulcerations, and secondary bacterial infections also have been reported with use of this agent. Imiquimod poses little risk of scarring when used to treat facial warts.

Unfortunately, these results have not been replicated in any controlled trials to date, and, anecdotally, practicing physicians are not able to achieve the same results. The study has a number of flaws, including the small sample size, gentle freezing of the wart, the high dropout rate, and the reliance on telephone interviews to assess treatment efficacy.

Nevertheless, the technique still may have merit, with some modification. For example, some experts have suggested that liquid nitrogen should be applied for at least 20 seconds—twice as long as the 10-second bursts used in the study.

Salicylic Acid

Before parents consult their pediatrician or family physician about a child’s wart, it is common for them to try at least one over-the-counter wart treatment containing salicylic acid.

Multiple placebo-controlled studies have been conducted on the efficacy of salicylic acid in the treatment of warts. A recent review of placebo-controlled trials published between 1966 and 2003 showed that this FDA-approved wart therapy yielded an average clearance rate of 75% compared to 48% seen in placebo-treated groups; although these cure rates are highly variable depending on the particular study design, with efficacy as low as 50% having been seen in some studies.

Treatment in the Dermatologist’s Office

If an adequate trial of therapy—up to 4 months—fails to produce the desired response, the dermatologist can offer additional modalities that may prove successful.

Oral Immunotherapy

Studies have demonstrated that oral cimetidine alone and in combination with levamisole may be effective treatment for warts, including genital warts, in children. The dose of cimetidine in these studies was 30 to 40 mg/kg/day for 3 months. The usual dose of levamisole was 150 mg daily on two consecutive days on a weekly basis during cimetidine treatment. Cimetidine, available without prescription, works through the cytochrome p450 system, so families need to be informed of the significant risk for drug interactions. Levamisole can cause leukocytopenia or skin necrosis and should be accompanied by regular measurement of blood counts. It also should be reserved for the most severe cases in children. Levamisole increases the CD4 to CD8 ratio, promoting immunomodulatory effects on cell-mediated immunity. Cimetidine treatment is painless, but the liquid has an unpleasant taste; it may be flavored to make it more palatable for children.

Two other immunotherapies that are used to treat warts in children are squaric acid diphosphopropenone (DAPB) and dibutyl ester in acetone (SADBE). SADBE is designed for home use by parents, but DCP should be applied by a physician. With SADBE,
complete clearance rates of 58% have been reported with home use\textsuperscript{13} and 68% with in-office use.\textsuperscript{14} Clearance rates of up to 90% have been reported with DCP.\textsuperscript{15} Either drug has been shown to be more effective when applied after the warts have been first treated with 70% salicylic acid in petrolatum at home.

Relapse of cleared warts is uncommon with either of these immunotherapies. Side effects may include urticaria or severe eczematous reactions, necessitating discontinuation.

Immunotherapy for warts may work by one or more of a variety of pathways. One theory being promoted is that these agents may cause a shift from a T helper type 1 (Th1) cell response to a Th2 response, which augments non-specific cellular immunity. Non-specific irritation may induce proliferation of immune cells, thereby increasing antigen recognition.

**Injected Immunotherapy**

Another approach to immunotherapy that has been studied in children involves a mildly painful intralesional injection of either mumps or Candida antigens. In a study of 47 patients,\textsuperscript{16} injected immunotherapy was less effective in children than it had been in adults because the children had a less intense cell-mediated response to the antigens. Further study is needed to assess the usefulness of this modality in children.

**Laser Therapy**

Pulsed-dye laser, which may target the wart’s vascular supply—is useful for destruction of recalcitrant warts in children, particularly thin, periangual warts. Pain can be minimized by pretreating the area with topical lidocaine. Carbon dioxide laser is a less reliable laser for the treatment of warts in children and may lead to scarring.

**Conclusion**

If warts are asymptomatic and are in a location that causes no cosmetic or other problems, observation is the ideal management course, as most warts will resolve spontaneously within 3 years. However, most parents and children prefer treatment for their warts.

**The estimated 25% of warts that resist treatment in the pediatrician’s or family practitioner’s office may require therapy with a combination of topical agents followed by electrodessication, cryosurgery, and/or pulsed-dye laser.**

The ideal treatment of warts in children is one that is both effective and painless. When over-the-counter remedies (such as salicylic acid) fail to destroy lesions, topical treatments such as 5% 5-FU and imiquimod have both been shown to meet those two criteria, in many cases. Topical medications offer ease of administration and the benefit of home application. Efficacy seems to be enhanced when these agents are used under occlusive tape, such as duct tape.

The estimated 25% of warts that resist treatment in the pediatrician’s or family practitioner’s office may require therapy with a combination of topical agents followed by electrodessication, cryosurgery, and/or pulsed-dye laser.

**References**


Management of Warts in Pediatric Patients

There is no fee to participate in this activity. Please forward the Test Answer Sheet and Evaluation Form to:
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Instructions: For each question or incomplete statement, one answer or completion is correct. Four of five correct responses are required for credit. Circle the most appropriate response.

1. Warts are resistant to treatment in ___ of cases.
   a. 25%
   b. 33%
   c. 50%
   d. 70%

2. The warts that are spread from infected mother to baby during birth are most commonly due to infection with which subtypes of human papillomavirus?
   a. HPV-16, HPV-18
   b. HPV-1, HPV-2
   c. HPV-6, HPV-11
   d. HPV-30, HPV-33

3. Which of the following types of warts in young children require referral to a dermatologist?
   a. Flat warts on the face
   b. Genital warts when sexual abuse is suspected
   c. Plantar warts
   d. Those that show pinpoint bleeding when the surface is pared away

4. Within 2-3 years, about two thirds of common warts:
   a. Resolve without treatment
   b. Recur
   c. Are spread to other parts of the child’s body
   d. Develop pigmentation

5. A feature that distinguishes warts from calluses and corns is:
   a. Anatomic site
   b. Coloration
   c. Pinpoint bleeding when the surface is pared
   d. Presence of hyperkeratosis

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