Non-genital Warts: A Review of Current Treatments Part II

When determining which treatment modality to choose in treating non-genital warts, there are several factors to consider, including the convenience of the treatment, patient discomfort, location of warts and potential side effects.

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Last month’s article explored the possibilities for the physical destruction of non-genital warts. It reviewed literature on various procedures, such as cryotherapy, electrosurgery, laser removal, and duct tape occlusion. Each of these approaches has been shown to yield different results under different circumstances. Another type and sometimes necessary approach to wart removal is chemical destruction. This article will examine the options available for chemical destruction, reviewing data for various procedures and weighing their benefits. It will also explore immunological approaches to wart destruction.

Chemical Destruction

Salicylic Acid. Salicylic acid is one of the two most commonly used treatments for warts. Various preparations of salicylic acid are available commercially. Over-the-counter preparations are usually less than 17% salicylic acid, however, there are a few OTC products that contain 40 percent. Physician-prescribed preparations can contain as much as 70 percent salicylic acid. Due to lack of data, comparing individual products is not possible. Treatment response rates of 40 to 84 percent (with an average of 61 percent) have been reported. The therapeutic benefit of topical therapies containing salicylic acid—whether over-the-counter or prescription—is supported by evidence from randomized controlled trials (RCTs). There is consistent evidence that topical salicylic acid is an effective therapy for non-genital cutaneous warts.17

One study reviewed 13 trials that assessed topical salicylic acid. Various preparations were used. Only one trial used 60 percent salicylic acid; the rest used standard preparations of between 15 percent and 26 percent with or without lactic acid. Minor skin irritation was reported occasionally in some of the other trials, but generally there were no major harmful effects of topical salicylic acid.8

The Cochrane review identifies topical therapy with salicylic acid as safe and effective and reports that no

Take-Home Tips. Many treatment options for non-genital warts are considered off label. Despite numerous treatment options, there is still no consensus on a single, first-line treatment, and many treatments lack consistent evidence to support their use. Continued vigilance is warranted; however, some uses are supported by a reasonable body of scientific evidence, and others are based on anecdotal support, clinical judgment or habit based on recycled dogma that is supported by little or no data.
clear evidence exists to prove that other therapies have an advantage in regard to higher cure rates or fewer adverse effects. The pooled data from six RCTs demonstrated a cure rate of 75 percent in those treated with salicylic acid compared with 48 percent in the control group. Another guideline lists salicylic acid as the first-line therapy for warts on the face, plantar warts, and flat and common warts on the hands.17

One account reports topical 17% salicylic acid was the second most frequent modality used for warts behind liquid nitrogen cryotherapy. Of the 13 patients who used topical salicylic acid, five used it in combination with liquid nitrogen. Three of the patients showed complete clearance—two in combination with liquid nitrogen and one using salicylic acid only.3

Salicylic acid is easily accessible over the counter, is inexpensive, and easy for patients to use. Disadvantages of salicylic acid use are patient adherence requirements, daily application by patient, and delayed response times. Cost of treatment is minimal to the patient and to the healthcare system as a whole.17 A systematic review of local treatments of cutaneous warts by Mitsuishi et al., found evidence that topical treatments with salicylic acid have a therapeutic effect, with a cure rate of 75 percent compared with 34 percent in placebo controls.3

80% Phenol in Solution. Phenol (carbolic acid) is a caustic agent that produces a white eschar on the surface of the skin and can penetrate deep into the tissue.1 Phenol is a protoplasmic poison. A dilute solution (0.5%-2%) decreases itch by anesthetizing the cutaneous nerve endings. It has been used for treatment of ingrowing nails and molluscum contagiosum with efficacy. Phenol solution 0.5% has also been used for treatment of reactive perforating collagenosis. It has not been used for warts to date. Phenol is readily available and simple to use, but it should not be diluted as this increases its absorption and potency. It should not be used in pregnant women and in extensive areas. Treatment with 80% phenol is statistically insignificant over liquid nitrogen cryotherapy.3 Other agents used for chemical destruction are monochloracetic acid, dichloracetic acid, trichloroacetic acid, and silver nitrate.

A single-blinded clinical trial study evaluating the clinical efficacy of 80% phenol solution in the treatment of common warts found that complete clearance of warts after six weeks was achieved in 70 percent of patients who were treated with cryotherapy, and 82.6 percent of patients in the 80% phenol group; there was no statistically significant difference between the two methods. Complications included pain, hyperpigmentation, hypopigmentation, burning sensation and erythema. The percentage of cure rate was higher in the 80% phenol group, but this difference was not statistically significant.5

Cantharidin. Cantharidin is secreted by many species of blister beetle, most notably by the ‘Spanish fly’ (Lytta vesicatoria). Cantharidin inhibits protein phosphatases 1 and 2A (PP1, PP2A). Blister beetle has been used in Asian traditional medicine to treat Molluscum contagiosum virus (MCV) infections and associated warts and is now also used for cancer treatment. Cantharidin content varies among individual blister beetles as well as among different species.22 Data suggests that cantharidin causes both DNA single-and double-strand breaks. In light of this data, it is believed cantharidin treatment causes oxidative stress that damages DNA and triggers p53-dependent apoptosis.5

Immune Modulators
Immunotherapy has many advantages, including the ability to treat many lesions simultaneously, and the reduction in frequency and size of relapsing warts. An immune mechanism seems to be confirmed by the fact that untreated warts can also be rejected. Immunotherapy with diphenylcycloprenone (DPCP) should not be used routinely as an initial therapy for facial warts, but is a possible alternative in selected patients with recalcitrant multiple facial warts.6 Forms of immune modulators include imiquimod, intralesional immune modulators, contact immunotherapy, cimetidine, zinc, and retinoids. Because wart proliferation is controlled by the immune system, various methods have been used to stimulate the immunologic response to HPV. Among these are topically applied inorganic molecules capable of eliciting contact hypersensitivity, such as imiquimod and intralesional interferons.9

Wart Therapy: Chemical Destruction

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Imiquimod. Imiquimod (Aldara/Zyclara, Graceway) is a low-molecular-weight, toll-like receptor (TLR) agonist that is a synthetic nucleoside analog which sensitizes the host’s inflammatory response to viral infection and neoplastic cutaneous lesions.\textsuperscript{23} Imiquimod (Aldara/Zyclara) is easy for patients to apply at home three times a week. Side effects may include erythema, pruritus, erosions and bacterial infections. Cost is significantly greater than salicylic acid but less than cryotherapy and pulsed dye laser.\textsuperscript{17} Although randomized controlled trials are lacking, imiquimod has demonstrated potential efficacy in the treatment of recalcitrant non-genital warts. In a study using imiquimod, cure rates of 88.9 percent were observed for recalcitrant non-genital warts in children when applied twice daily. The duration of treatment ranged from two to 12 months with a mean duration of 5.8 months. A small separate study demonstrated similar results. Imiquimod was applied once a day and occluded for a total of four weeks; of the 10 study participants, nine demonstrated complete clearance of recalcitrant common warts.\textsuperscript{17}

According to Gaspari et al., systemic adverse events of treatment across clinical trials were less than 10 percent. Adverse events experienced included fatigue, nausea, headache and myalgia. Severe flu-like symptoms were found to be uncommon. The most common adverse events reported are mild to moderate application-site reactions. Rare application site reactions such as persistent post-inflammatory pigmentation alteration, alopecia, and rapid, heavily crusted erosions have been reported.\textsuperscript{23}

Many of the molecular effects of imiquimod can be explained by the reprogramming of gene expression mediated by the TLR-7 signaling pathway, which causes the movement of the transcription factor nuclear factor kappa \( \beta \) (NF-k\( \beta \)) to the nucleus of a cell activated by this TLR agonist. This single transcription factor is responsible for the up-regulation of hundreds of different genes involved in the inflammatory process, including, but not limited to interferon-alpha (TNF-alpha) and interleukin-12 (IL-12). Some of these up-regulated cytokines may enhance apoptosis of neoplastic or infected epidermal cells and up-regulate DNA repair enzymes following ultraviolet-induced (UV) nucleic acid damage. Furthermore, imiquimod enhances professional antigen-presenting cells (APCs) antigen presentation to T cells. Imiquimod is a potent immunological adjuvant that bridges innate and adaptive immunity by directing and enhancing the cellular immune response to viral infection, tumor formation, fibrotic conditions and some degenerative conditions.\textsuperscript{23}

Randomized controlled trials are warranted to further examine the efficacy of imiquimod for non-genital warts. One review based on non-randomized historical cohort comparisons supported the use of imiquimod as first-line therapy for treatment of flat warts. Another review, however, found insufficient evidence to support the use of imiquimod for treatment of cutaneous non-genital warts.\textsuperscript{17} Gaspari et al. (2009), states currently there are anecdotal and observation reports, with some randomized studies, which suggest wide-ranging clinical potential for imiquimod and related molecules.\textsuperscript{23} Topical imiquimod has Food and Drug Administration approval for genital warts, however, it also has been reported to have utility in the treatment of non-genital warts.\textsuperscript{9}

Gaspari, et al. concludes that imiquimod elicits a multifaceted immune response, and combining imiquimod with other treatment modalities (particularly ablative treatments) further improved clinical efficacy in some conditions. This is true for currently approved indications as well as selected off-label uses.\textsuperscript{23}

Intra-lesional Immune Modulators. Intralesional immunotherapy for common warts is effective and safe. It is unique in affording many patients a therapeutic response in untreated warts and may, through stimulation of HPV-directed immunity, provide fewer recurrent warts. While useful in any patient with warts, intralesional immunotherapy may be particularly useful in patients with numerous lesions or lesions covering large surface areas. Repeated observation of untreated warts resolving after injection of only one wart prompts the speculation that intralesional immunotherapy induces HPV-directed immunity. What factors determine response or resistance to therapy is unclear.\textsuperscript{9}

The first group of intra-lesional immune modulators is intra-lesional interferons. Interferon alfa-2b is a
intra-lesional interferon approved by the Food and Drug Administration for the treatment of condyloma, requiring twice-weekly injection for three weeks for optimal results.\textsuperscript{9} One study comparing interferon alfa-2b with saline alone evaluated patients with more than one wart receiving antigen (antigens given were either: Candida, mumps, or Trichophyton) with or without concomitant interferon injection, were statistically more likely to experience resolution of untreated and anatomically distinct warts. The addition of interferon alfa 2-b to antigen did not significantly improve response. There was no significant difference between interferon alfa-2b and saline.\textsuperscript{9}

Immune modulator treatments for non-genital warts with intra-lesional interferons are rarely used today. Most of the trials reviewed were from the 1970s and 1980s. Evidence provided by all the trials was limited by the heterogeneity of the methods and design. Overall, treatment was not strikingly effective.\textsuperscript{8}

The second group of intra-lesional immune modulator treatments, which employs the ability of the immune system to recognize certain viral and fungal antigens, is mumps, Candida, or Trichophyton. It is believed that the delayed-type hypersensitivity reaction induced by these antigens increases the ability of the immune system to recognize and clear HPV. The most common side effect is itching at the injection site. Other side effects included an influenza-like illness that can last less than 24 hours and usually improves with non-steroidal anti-inflammatory drugs.\textsuperscript{17} Intralesional immunotherapy using mumps, Candida, or Trichophyton skin test antigens have proven efficacy in the treatment of warts.\textsuperscript{9} Candida skin test is generally more commonly used than other antigens.\textsuperscript{17}

Horn, et al. reports that researchers have shown the effectiveness, in the treatment of common warts, of intra-lesional injection of antigen preparations of mumps, Candida, or Trichophyton. In one study reviewed by Horn, 74 percent of subjects receiving immunotherapy experienced resolution of untreated distant warts. Of subjects treated in the cryotherapy arm of the same study, 57 percent experienced resolution of the treated wart, while no distant wart responses occurred. In a separate report, the effectiveness of this treatment in children, in all of whom two treatment modalities had failed, 47 percent of subjects responded to immunotherapy and 34 percent cleared untreated distant and anatomically distinct warts.\textsuperscript{9} Bacelieri and Marchese Johnson state in one study complete resolution was demonstrated with Candida treatment of warts in 47 percent of the participants and 75 percent to 99 percent resolution in 13 percent of the participants. In 34 percent of those enrolled in the study, complete clearance of all warts distant from the injection site was noted. In 22 percent of the study participants, clearance rates of 75 percent to 99 percent for distant warts also were noted. The regression of warts at distant sides has not been established with other therapies.\textsuperscript{17}

Intra-lesional bleomycin (0.1% solution with concurrent anesthetics) is the final type of intra-lesional immune modulator treatment for non-genital warts. Bleomycin (Blenoxane), a chemotherapeutic agent, inhibits DNA synthesis in cells and viruses. Bleomycin is an alternative therapy for warts that have either not responded to other therapies or that may be difficult to surgically excise.\textsuperscript{17} Intra-lesional bleomycin has been used abroad since the 1970’s but is considered a relatively new treatment in the United States. Although there is controversy about the efficacy of bleomycin, according to Dhar et al., most studies show lower cure rates for cryotherapy when compared with studies done on bleomycin. Intralesional bleomycin has shown cure rates ranging from 14 percent to 99 percent.\textsuperscript{18}

Pain is the major limiting factor to treatment with bleomycin. Potential side effects include scarring, change in pigmentation, nail damage, and Raynaud’s phenomenon. Bleomycin is listed as pregnancy category D, given its potential for significant absorption following injection. Following application of a topical anesthetic, bleomycin is placed on the wart and “pricked” into the wart using a needle. After the initial injection, subsequent injections can be given every three to four weeks until clearance is achieved.\textsuperscript{17}

Among published reports, there is no consistent evidence for efficacy of intralesional bleomycin. Dhar et al. compared intralesional bleomycin to cryosurgery and found it to be significantly more effective than cryosurgery for the treatment of cutaneous warts. Recurrence was found to be 13 percent in bleomycin-
treated warts and 23 percent in cryotherapy-treated warts, but differences were regarded as statistically insignificant. The pain period in the bleomycin group was shorter than the pain and discomfort in the cryotherapy group. Dyspigmentation was observed in both treatment groups in a significant proportion of patients. More marked dyspigmentation was seen in cryotherapy groups, due to greater post inflammatory reaction. Patients required shorter courses of therapy in the case of bleomycin therapy. Thus, if group treatment can be arranged, the cost of bleomycin therapy will be significantly minimized. The researchers found that intralesional bleomycin was significantly more effective than cryotherapy and was a safe alternative for the treatment of cutaneous warts.18

Regardless of the many available studies on bleomycin and cryotherapy in treating warts, little head-to-head research has been done to compare efficacy of these treatments. Another study compared the therapeutic effects of intralesional bleomycin and cryotherapy on common warts of the hands and feet. Each patient received both cryotherapy and intralesional bleomycin on their warts. The two treatment types were randomly allocated to either right sided or left sided warts. In 86.4 percent of the cases, warts on the limb side treated by intralesional bleomycin were cleared compared with 68.2 percent for cryotherapy. Bleomycin was found to have a clearance rate equal to 87.6 percent of warts, compared to 72.3 percent by cryotherapy.24

The number of RCTs that demonstrate the efficacy of bleomycin is low, but one review has concluded that there is fair evidence to support its use for recalcitrant hand and plantar warts. The Cochrane review states that there is no consistent evidence for the effectiveness of intralesional bleomycin for treatment of non-genital cutaneous warts, and the data could not be meaningfully pooled for analysis. Another review, based on four RCTs and multiple case series that provide evidence of the effectiveness of bleomycin, recommends its use as a third-line therapy for common and plantar warts.17

Gibbs et al., found no consistent evidence for the effectiveness of intralesional bleomycin in review of five trials. Four of the trials, with widely varying results, used warts rather than individuals as the unit of analysis and could not be meaningfully pooled. Cure rates in all five studies ranged from 16 to 94 percent. Two trials showed higher cure rates with bleomycin than with placebo, one showed no significant difference between bleomycin and placebo, and one showed higher cure rates with placebo than with bleomycin.8

One trial reported adverse events in 31 percent of participants but did not specify what the adverse events were or their distribution between the active treatment and placebo groups. None of these trials provided precise data on adverse effects. Pain was reported in most participants, local anaesthetic was used routinely before the injection of bleomycin to increase tolerability of treatment. One trial reported pain in most participants irrespective of dose. In another trial, two of 24 participants receiving bleomycin withdrew either because of the pain of the injections or because of pain after the injections.8

Contact Immunotherapy. Contact immunotherapy, which is believed to work for the treatment of warts by inducing a type IV hypersensitivity reaction. This cell-mediated response is believed to act against a complex of contact agent hapten bound to protein of viral or human origin with the Langerhans cell as the site of antigen formation and presentation. This results in the disappearance of the wart when the contact agent is applied, enhancing spontaneous wart regression.10

Induction of a type IV hypersensitivity reaction has been achieved with Dinitrochloro-benzene (DNCB), diphenylcyclopropenone (DPCP), and squaric acid dibutylester (SADBE). This reaction is utilized to treat warts. These easily available agents, which can sensitize at least 95 percent of normal individuals, are not easily found in human environments, are chemically stable, inexpensive, and have few adverse effects.10

The first type of contact immunotherapy to discuss is Diphenylcyclopropenone (DPCP). In order to analyze the efficacy and side effects of DPCP treatment of viral warts, a prospective study was designed to follow six patients with chronic and resistant facial warts through immunotherapy sensitization with DPCP for 10 weekly sessions. Patients were first sensitized with 2% DPCP and then followed by weekly maintenance
of 0.001-1% DPCP in acetone on facial warts until mild contact dermatitis was obtained. After application of DPCP to the warts of the face, all of the facial warts became inflamed and resolved.

At the end of the investigation, the complete response was 66.6 percent, and side effects were not a problem in the majority of patients. Adverse effects for treatment with DPCP included moderate to severe reactions at sensitization site or at the treatment site, or spreading of contact eczema to other parts of the body. DPCP appears to be a valuable, safe, and well-tolerated treatment for resistant and chronic facial warts.

The second type of contact immunotherapy to discuss is squaric acid dibutylester (SADBE). DPCP and SADBE have been found to be less stable than DNCB. DPCP requires shielding from light, and SADBE requires refrigeration. Both SADBE and DPCP have been shown to be non-mutagenic by the Ames test, whereas DNCB is mutagenic by the same standard. SADBE tends to be more expensive than DPCP and DNCB.

Lee and Mallory, sensitized patients with 0.5% to 1% SADBE, which was applied directly to the warts during office visits scheduled every two to four weeks. A concentration of 0.5% SADBE was used on warts in sensitive areas such as the perianal region and on warts of patients who experienced an exuberant contact dermatitis. After several treatments, if no change was noted in the warts, the applied concentration of SADBE was increased to two percent and occasionally to five percent. Squaric acid was not applied to the face. Instead, facial warts were treated with cryotherapy.

Two previous studies on the use of squaric acid dibutylester (SADBE) for warts have reported widely divergent cure rates (10 percent and 60 percent). Clearing of all warts was seen in 69 percent of patients, improvement in 10 percent, and no change in 21 percent. For the cured patients, mean duration of treatment was 4.2 months (range: one to 12 months) and mean number of treatments was 5.7 (range: two to 15). The main adverse effect of SADBE is acute contact dermatitis, although dyshidrosiform hand dermatitis has been reported. All three agents have been shown to be effective against warts, with cure rates of 69 to 91 percent for DNCB, 62 percent for DPCP, and 60 percent for SADBE.

**Cimetidine.** The final group of immune modulator treatment for non-genital warts is cimetidine, oral zinc sulphate and systemic retinoids. Cimetidine and oral zinc sulphate have important effects on the immune system and are utilized as immunomodulators in the treatment of various diseases. Systemic retinoids have been used to treat warts because of their ability to alter keratinization and induce an irritant dermatitis thereby accelerating the clearing of warts.

Cimetidine is an H2 receptor antagonist that has immunomodulating effects. In general, cimetidine promotes cellular immunity by activating natural killer (NK) cells, eliciting an increase in IL-2 production. Cimetidine also promotes the expression and subsequent release of IL-12 from monocytes or macrophages in vivo and may enhance T helper (Th) cells and NK cell activity, and the production of IL-2 and interferon (IFN)-γ. IFN-γ is produced not only by NK cells but also by Th 1 cells. While IL-18 stimulates IFN-γ production by Th cells and by NK cells, there is limited information on the contribution of this to immunity in patients with various infectious diseases.

Cimetidine has been shown to improve various types of human neoplasms and more recently it has been shown to be effective in treating recalcitrant or multiple viral warts in some reports. However, it is not well understood why cimetidine is effective on viral warts. One study investigated 55 patients with multiple viral warts treated only with oral cimetidine for up to four months to examine efficacy of treatment. As a result, 34.5 percent of the patients had a dramatic clinical improvement or complete remission of their viral warts, and 23.6 percent of the patients had partial responses within four months of cimetidine therapy. Their results show the higher dose of oral cimetidine was more effective in treating multiple viral warts. The results suggest that cimetidine is an effective treatment for viral warts. In addition, based on the decrease in IL-18 mRNA elicited by the drug, IL-18 might be expressed by keratinocytes infected with HPV.

Due to their short plasma half-lives, H2 receptor antagonists may be administered in relatively high
doses of 30-40 mg/Kg/day divided into one or two times a day to provide effective therapy. In 2003, Mitsuishi reported that recent investigations recognized the immunological effects of high or low doses of cimetidine against multiple or recalcitrant warts. Those reports have suggested that cimetidine, through various immunodulating mechanisms, can lead to the remission of viral warts.

Cimetidine has been used in children and adults to treat warts, but has shown conflicting results. Several studies have not demonstrated better results with cimetidine compared to placebo. The incidence of adverse effects reported was low and included nausea, epigastralgia, diffuse pruritus and pain at lesion sites.

**Zinc Sulfate**
Zinc sulfate is used as an immune modulator therapy for the treatment of warts. Zinc deficiency determines thymic hypoplasia with repercussion on T cell maturation, resulting in immune deficiency that favor associated infections. Elemental zinc dosage is suggested at 2.5mg/Kg/day (maximum 150 mg/day). Pharmacological doses of 4 to 12mg/Kg/day of elemental zinc may induce gastroenteritis, gastrointestinal bleeding, microcytosis, relative neutropenia and hypoceruloplasminemia. Prolonged zinc use may induce copper deficiency and anemia, which resolves with discontinuation of zinc. Zinc sulfate seems to be easier to tolerate than zinc acetate or gluconate. One 100mg capsule of zinc sulfate has 22.5 mg of elemental zinc.

Stefani, et al. conducted a randomized prospective double-blind study and concluded that 10mg/kg/day zinc sulfate does seem to be more effective than cimetidine for the treatment of children and adults with multiple and difficult to handle warts. They observed significant difference in the proportion of clinical response between the two studied groups. However, the small number of patients did not enable any definitive conclusion. The use of cimetidine produced poor results and lead to only partial clearance in some patients. Adverse effects reported were nausea, vomiting and diarrhea. Side effects may be reduced by dividing the total dose into three daily doses to be taken with meals.

**Retinoids.** Both oral retinoids and systemic retinoids can be used as immune modulator therapy for non-genital warts. According to Bacelieri and Marchese Johnson, one review found fair evidence supporting the use of topical retinoids using a number of case reports and a limited number of trials of systemic retinoids. Another review of several case studies recommended oral and topical retinoids as second-line therapy for the treatment of flat warts.

A small study examined the efficacy of etretinate in children with extensive warts. A dose of 1mg/Kg/day of etretinate was given for no longer than three months. Of the 20 children involved in the study, 16 demonstrated complete clearance of their warts without relapse. Warts recurred in four patients following partial regression. Etretinate is no longer available in the United States; acitretin (Soriatane) is used now.

**Conclusion**
Many treatment options for non-genital warts, like many dermatological treatments, are considered off label. Despite numerous treatment options, there is still no consensus on a single, first-line treatment, and many treatments lack consistent evidence to support their use. The most common treatment modalities for warts include physical destruction, chemical destruction, immunomodulators, and tape occlusion.

Current data is neither sufficient to rule out nor determine a standard of care for any of the above treatment options. Continued vigilance is warranted; however, some uses are supported by a reasonable body of scientific evidence, and others are based on anecdotal support, clinical judgment or habit based on recycled dogma that is supported by little or no data. Wart treatment presents many challenges for management and cure of this cutaneous viral infection. Topical treatment and physical destruction are widely used in dermatology for treatment of warts. There is no perfect non-genital wart treatment, so both clinicians and researchers must continue to establish optimal treatment regimens.

Although it is widely believed that cryotherapy may succeed when topical salicylic acid has failed, the studies revealed no clear evidence to support that contention, as discussed in last month’s article. Indeed,
some evidence shows that, at best, cryotherapy is only equal in efficacy to topical salicylic acid.\(^8\) Cryotherapy is one of the more commonly used procedures in physician’s offices for treatment of the common wart. While it is a useful procedure for the treatment of warts, it causes fear and discomfort for many children.\(^4\) Evidence supports use of over the counter salicylic acid and physician administered cryotherapy.\(^7\)

Photodynamic therapy and use of pulsed dye lasers may hold promise for the future. Long pulsed Nd:YAG laser is safe and effective for the removal or reduction of warts and is less dependent on patient compliance than are other treatment options.

Many patients with multiple warts have defective cell-mediated mechanisms, making treatment with various immunomodulators ineffective. In general, intraleional bleomycin has been shown to be more effective than cryotherapy in treating warts on the hands and feet.\(^6\)

SABDE treatment is worth considering in patients with recalcitrant warts, especially in those who do not tolerate painful procedures well.\(^10\) Topical immunomodulator with agents such as dinitrochlorobenzene is currently best confined to specialist centers given its adverse effects.\(^8\) Considering the ethical problems arising from the use of substances whose long-term effects are still unknown, Aghaei, et al. has only used DPCP in treating resistant and multiple facial warts as a last resort after the failure of other treatment.\(^6\)

Although the immune-based mechanism of imiquimod is not HPV-type-specific, it has been reported that imiquimod 5% cream may be effective in infections with HPV subtypes that cause non-genital warts.\(^17\)

Duct tape therapy should be considered due to increased likelihood of compliance, primarily due to the ease of administration. Another benefit of tape occlusion therapy is that it is much less costly than cryotherapy. The treatment can be undertaken in the home using simple inexpensive duct tape. Finally, tape occlusion therapy appears to be less threatening to a young child than freezing.\(^4\)

The absence of high quality evidence prevents the rational use of treatments for common warts.

Evidence supports the use of simple topical treatments containing salicylic acid, which seem to be both effective and safe. No clear evidence suggests that any of the other treatments have a particular advantage of either higher cure rates or fewer adverse effects.\(^8\) Every treatment decision should be made on a case-by-case basis according to the experience of the healthcare provider, patient preference, and the application of evidence-based medicine.\(^7\)