

# An Armamentarium of Wart Treatments

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Patients and clinicians experience the frustration of cutaneous viral warts caused by infection with the human papilloma virus (HPV). Warts appear in various forms on different sites of the body and include common warts (*verruca vulgaris*), plane or flat warts, myrmecia, plantar warts, coalesced mosaic warts, filiform warts, periungual warts, anogenital warts (venereal or condyloma acuminata), oral warts and respiratory papillomas. Cervical infection with HPV is now known to cause cervical cancer if untreated. A review of the medical literature reveals a huge armamentarium of wart monotherapies and combination therapies. Official evidence-based guidelines exist for the treatment of warts, but very few of the reported treatments have been tested by rigorous blinded, randomized controlled trials. Therefore, official recommendations do not often include treatments with reportedly high success rates, but they should not be ignored when considering treatment options. It is the purpose of this review to provide a comprehensive overview of the wart treatment literature to expand awareness of the options available to practitioners faced with patients presenting with problematic warts.

**Keywords:** Bleomycin; Cantharidin; Cryotherapy; Diphencyprone; Human papilloma virus; Imiquimod; Laser; Vaccine; Virucidal; Wart

Common warts have been a frustration for both patients and clinicians since early Greek and Roman times.<sup>1</sup> They can greatly affect a patient's quality of life by causing embarrassment, fear of negative appraisal by others and frustration caused by persistence and/or recurrence. Moderate to extreme discomfort is reported in 51.7% of patients, and social or leisure activities are affected to a moderate to extreme degree in 38.8%.<sup>2</sup>

Warts of the genital tract carry a much more ominous and pernicious threat for women in particular. It has been estimated that up to 70% of sexually active women become infected during their lifetime with human papillomavirus (HPV), the infective agent that causes warts.<sup>3-5</sup> A causal role for HPV infections in cervical cancer has been documented beyond reasonable doubt. HPV DNA is present in virtually all cervical cancer cases worldwide, with it being detected in 99.7% of an international series of cervical cancers by genetic amplification techniques and in 100% of cases as confirmed by histological review.<sup>6,7</sup> Cervical cancer is the most frequent common cancer in developing countries and the second most common cancer in women worldwide.<sup>3</sup> The

association between HPV infection and cervical cancer is so strong that HPV is now considered the first positive cause of any human cancer ever identified.<sup>3</sup>

This raises the level of concerns over HPV prevention, screening and treatment from that of a nuisance condition to that of a major public health concern. Attention is beginning to focus on the viral factors that determine persistence and neoplastic progression to cancer and the possible role of HPV in other nongenital cancers (e.g., skin, upper aerodigestive tract).<sup>8-17</sup>

Patients with warts seek advice from general practitioners, pharmacists, naturopaths, allied health professionals, family or friends, dermatologists, gynecologists, obstetricians and pediatricians for treatment and may present with recalcitrant warts that have been previously treated with anything from folk remedies to hypnosis to over-the-counter medications to more aggressive clinic-based treatments. Unfortunately, even with years of medical literature on this subject, high-quality, level I evidence for the efficacy of almost all treatments is nonexistent.<sup>18-23</sup> No treatment has yet proven 100% effective for a cure. Almost all treatments have some effect in most

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cases. Pain related to treatment, side effects and costs can be determining factors in choosing a therapy.<sup>24</sup> Even with a single agent, reported efficacies often vary widely and can depend on the patients' ages, compliance and immuno-competence, wart location, form and duration of presence, method of application and skill of the technician. The number of permutations of possible variations in treatment is vast and probably accounts for the lack of good evidence for any one therapeutic regimen.

Evidence-based reviews with guidelines have been published,<sup>18-20,25-29</sup> but these do not cover newer developments or therapies that have yet to be subjected to large, rigorous, blinded, randomized, controlled clinical trials. Simply because a therapy has not been subjected to such rigorous scientific testing does not mean that it is not worth knowing about or worthy of a cautious attempt in difficult cases. Warts have a maddening tendency to either disappear spontaneously making it difficult to know whether the treatment caused the cure, to recur after an apparent total clearance, or to be entirely recalcitrant to all treatments tried. Here we give a brief background of the etiology and pathobiology of HPV and then present a comprehensive list of the therapies and combinations that have been reported in the medical literature.

### **Etiology**

HPV is a double-stranded DNA virus that causes cutaneous viral warts, most commonly located on the skin and genitalia.<sup>30</sup> Minor abrasions and infections promoted by maceration of the epithelia most frequently serve as conduits for HPV to the basal keratinocytes, the primary targets for HPV infection.<sup>31,32</sup> A variety of different strains and variants of HPV have been identified based on DNA studies and serological detection of type-specific antibodies against HPV capsid antigens. Over 118 types of papillomavirus have been identified.<sup>33</sup> Different HPV types show a preference for either uncornified mucous membranes or cornified stratified squamous epithelium.

The most common warts on the hands and feet are caused by HPV types 1, 2, 4, 27 and 57.<sup>19</sup> More than 35 types of HPV infect the genital tract.<sup>33</sup> Types 6 and 11 are associated with low risk anogenital warts, and types 16, 18, 31, 33, 45 and 59 are most commonly associated with squamous cell and adenocarcinomas of the cervix.<sup>3,6,34-37</sup> Individuals are likely to be infected by multiple types.<sup>38,39</sup> The different types can behave synergistically to facilitate concurrent or subsequent infection with another type. Others can act antagonistically to interfere with one another.<sup>40</sup> Viral activity likely depends on the immune status and response of the infected individual.<sup>41</sup> Seroconversion after natural infection is a relatively slow process and is dependent upon viral load or persistent infection.<sup>42</sup> Recurrence after clinical cure is often due to latent virus versus reinfection.<sup>1</sup> The presence of HPV DNA in subclinical or latent forms can be detected by nested polymerase chain reaction and hybridization.<sup>1,43</sup>

Transmission of warts occurs from direct person-to-person contact or indirectly by fomites. Swimming pools and bathrooms are common areas for the spread of warts if the skin is macerated and touches rough surfaces.<sup>20</sup> Once HPV has infected the skin, autoinoculation can occur by scratching, shaving or traumatizing the skin.<sup>22,23</sup>

Nongenital warts occur in 7% to 10% of the general population, with the incidence peaking between the ages of 12 and 16 years.<sup>44</sup> Viral warts occur equally in both sexes in children ages 2 to 12 years and are among the three most common dermatoses treated.<sup>31,45,46</sup> Approximately 23% of warts regress spontaneously within 2 months, 30% within 3 months and 65% to 78% within 2 years.<sup>20</sup> Previously infected patients have a higher risk for development of new warts than those never infected.<sup>47,48</sup> The rate of clearance is influenced by factors such as viral type, host immune status, extent and duration of warts.<sup>1,44</sup>

### **Diagnosis**

The clinical picture of cutaneous warts differs by specific location on the body. *Verruca vulgaris* (common warts) are hyperkeratotic, exophytic and dome-shaped papules or nodules especially located on fingers, hands, knees, elbows or any other sites of trauma.<sup>31</sup> Plane or flat warts are flat topped papules with minimal scaling and only slight elevation and are 2-4 mm in diameter. Intermediate warts can show features of both common warts and flat warts. Myrmecia are large, deep, burrowing warts.<sup>49</sup> Plantar warts can be painful due to their callused, endophytic papules that have deeply penetrating sloping sides and a central depression.<sup>31</sup> Numerous coalesced warts on the plantar surface will form a tile-like pattern known as mosaic warts.<sup>22,23</sup> Filiform warts are most often seen on the face with characteristic frond-like projections that exhibit quick proliferation.<sup>22,23</sup> Periungual warts occur anywhere along the nail margins, including the proximal nail fold and hyponychium, which can subsequently lead to onychodystrophy from nail matrix damage and onycholysis from nail bed warts.<sup>50</sup> Nail biters commonly exhibit multiple periungual warts involving several nails.<sup>50</sup> Anogenital warts (venereal or condyloma acuminata) occur in the perineum and on the genitalia or in the genital tract and are one of the most common sexually transmitted diseases. They can be an indication of sexual abuse in children under the age of 3, but may be transmitted to the neonates of infected women.<sup>20,43</sup> HPV infections of the genital tract can also be transmitted to the respiratory tract of a newborn child causing juvenile-onset recurrent respiratory papillomatosis.<sup>51</sup> Oral warts are small pink or white papules on the oral mucosa.<sup>52-54</sup> The clinical appearance of warts varies with location, but they are easily diagnosed by a trained clinician.

### **Differential Diagnosis**

Warts are identified by a change in the regular papillary skin lines with independent vascular sources. When warts resolve, normal dermatoglyphics return.<sup>55</sup> Dilated capillaries in the wart bleed subsequent to shaving the hyperkeratotic surface.<sup>31</sup>

These capillaries help to differentiate warts from corns or calluses.<sup>22,23</sup> HPV can masquerade as a seborrheic keratosis, callus, corn, lichen planus, epidermal nevus, molluscum contagiosum or squamous cell carcinoma.<sup>56</sup> An irritated achrochordon may resemble a wart. The extremities may demonstrate acrokeratosis verruciformis or epidermodysplasia verruciformis in the form of verrucous papules. Syphilitic condylomata must also be kept in mind in the differential diagnosis of anogenital warts.<sup>57</sup> Amelanotic melanoma must also be considered in a persistent wart.<sup>31</sup> Genetic amplification techniques combined with genotyping can determine the specific HPV type(s) involved in the infection. However, knowledge of the HPV genotype in benign warts does not influence choice of therapy.<sup>20</sup>

### **Histopathology**

Warts are usually diagnosed by their clinical appearance, but a histological examination may need to be performed for warts resistant to treatment and for verrucous lesions in immunocompromised individuals. Histologically, a wart demonstrates acanthotic epidermis with papillomatosis, hyperkeratosis and parakeratosis with elongated rete ridges often curving towards the center of the wart. Dermal capillary vessels are prominent and may be thrombosed, and mononuclear cells may be present. HPV-associated papilloma are characterized by large keratinocytes with an eccentric, pyknotic nucleus surrounded by a perinuclear halo (koilocytes). HPV infected cells may have small eosinophilic granules and diffuse clumps of basophilic keratohyaline granules and are not HPV particles. Flat warts have less acanthosis and hyperkeratosis and do not contain parakeratosis or papillomatosis, but they do have abundant koilocytes. Anogenital warts may express slight to extensive acanthosis and parakeratosis since they are within or adjacent to a mucosal surface and do not have a granular layer. Koilocytes are often observed in anogenital warts, and the rete ridges often form thick bands extending extensively into the underlying, highly vascular dermis.<sup>57</sup>

### **Treatment**

There is currently no cure for HPV infection, and therapy does not affect transmissibility.<sup>30</sup> Therefore, current therapy aims at eliminating signs and symptoms. No single treatment is fully effective in all patients. Different types of warts may need different site-dependent treatments, and treatments may need to be combined.<sup>20</sup> Spontaneous regression of warts must be considered in researching the effectiveness of treatment.<sup>20</sup> The ultimate wart treatment would resolve all or a great percentage of warts, be painless, need only one or a part of a wart treated, call for one to three treatments, create no scarring, offer HPV immunity for a lifetime and be available to all patients.<sup>56</sup> In 1995, the American Academy of Dermatology developed criteria for the indications for wart treatment<sup>56</sup> including: 1) the patient's desire for therapy, 2) symptoms of pain, bleeding, itching or burning, 3) disabling or disfiguring lesions, 4) large numbers or large sizes of lesions, 5) the patient's desire to prevent the spread of warts

to unblemished skin of self or others, and 6) an immunocompromised condition. Anogenital warts should receive special consideration and warrant vigilance for other sexually transmitted diseases.

For common warts, if receiving no treatment is acceptable to the patient, this is a viable option. However, warts are less likely to resolve spontaneously and are more resistant to treatment in adults, in immunosuppressed patients and in those with persistent warts.<sup>20</sup> An armamentarium of wart treatments exists, including over-the-counter treatments and therapies provided by primary care and dermatology offices. Because so few of the reported treatments have undergone rigorous clinical trials, rather than weighing the evidence for or against any particular treatment, we offer a comprehensive list of treatments that have been reported in the medical literature.

### **Folk and Alternative Remedies**

#### *Folklore*

Historic folk remedies have included many variants: "Rub a dusty, dry toad on warts, and they will disappear", or the advice of Tom Sawyer to "...back up against the stump and jam your hand in and say, 'Barley-corn, barley-corn, Injun-meal shorts, / Spunk water, spunk water, swallow these warts.'"<sup>58</sup> Before these remedies are scoffed at, they serve as a reminder that many warts resolve spontaneously regardless of the treatment or lack thereof.<sup>59</sup>

#### *Hypnosis/Suggestive Therapy*

For many years there have been sporadic reports of wart cures in both adults and children through hypnosis or autosuggestive therapy.<sup>60-66</sup> These are largely case reports or small case series with no controls for comparison with spontaneous regression rates. It is feasible that if hypnosis or suggestion could stimulate the immune system during therapy for wart treatment, as has been suggested in cancer cases, then there could be a basis for hypnotic benefits. However, this remains untested.<sup>67-69</sup>

#### *Garlic Extracts*

Components of garlic (*Allium sativum*) have been shown to have antiviral activity and to inhibit cellular proliferation of virally infected cells.<sup>70,71</sup> In one placebo-controlled trial, the application of chloroform extracts of garlic was reported to result in the complete resolution of cutaneous warts with no recurrence after 3-4 months.<sup>72</sup>

#### *Duct Tape*

Occlusive duct tape treatment was championed by Dr. Jerome Litt in a 1978 article.<sup>73</sup> This treatment has become popular again due to a journal article in 2002 by Focht et al comparing duct tape treatment with cryotherapy.<sup>74</sup> Their study included 61 patients aged 3 to 22 years being treated for common warts who were randomized to cryotherapy or duct tape arms of therapy. The cryotherapy treatment consisted of treatment every 2 to 3 weeks with a 10 second application of

liquid nitrogen for up to six treatments. The duct tape arm involved applying a piece of duct tape the size of the wart directly to the wart and removing it 6 days later. An emery board or pumice stone was then used to scrub the wart after soaking it in water. The wart was left open to the air overnight. The 6-day cycle was repeated the following morning. This process was repeated for up to 2 months.<sup>74</sup>

Warts completely resolved in 85% of the duct tape arm of the study versus only 60% in the cryotherapy group.<sup>74</sup> The mechanism by which duct tape acts remains speculative. Distant warts that were not treated with the duct tape also resolved, raising the possibility that the host's immune system was stimulated through local irritation produced by the duct tape. There were no reported side effects with using the duct tape, and most warts resolved within 1 month of treatment.<sup>74</sup> This is an optimal approach to treating children with warts, because it is painless and cost effective. More studies are required before this can be considered an evidence-based treatment, however.

### **Destructive Therapy**

Destructive therapy should not be confused with virucidal therapy. Destructive therapies are designed to damage or remove the lesion, rather than to kill the virus. These range from surgical curettage to cautery to caustic chemical ablation, and from cryotherapy to hyperthermic therapy. Many of the following approaches may be used with most warts. However, some warn against using destructive approaches for flat warts due to their tendency to Koebnerize.<sup>20</sup> It should be noted, however, that the reported phenomenon of peripheral wart spread around the margins of the traumatized wart represents either a seeding by HPV viruses or a failure to treat subclinical marginal infected tissues. Therefore, it is more properly categorized as a pseudo-Koebnerization.<sup>75-78</sup>

#### *Surgical Removal by Curettage or Cautery*

Surgical removal of warts by curettage followed by cautery was an early and still widely practiced method of treatment. Success rates of 65% to 85% have been reported, but scarring and recurrence occur in up to 30% of patients.<sup>79-82</sup> Scarring can be particularly problematic on the sole of the foot, so this technique is most commonly used for filiform warts on the limbs and face.

Surgical excision and cautery of warts is not recommended as a standard therapy because it can be painful and cause scars that are difficult to treat.<sup>83</sup> Like any destructive therapy, there is no assurance that the wart will not recur. Recurrence rates can be as high as 30%.<sup>20</sup> Recurrence has been attributed to the recrudescence of latent virus adjacent to the original wart.<sup>1</sup> No randomized, controlled trials for this treatment have been published.<sup>18</sup>

#### *Chemical Cautery*

Silver nitrate is probably most widely recognized in its historical use to prevent conjunctivitis in newborns,<sup>84</sup> but in

recent times it has largely been supplanted by antibiotic eye drops. The use of silver nitrate has also been used to chemically cauterize epithelial tissues in the treatment of pyogenic and umbilical granulomas, epistaxis, corns and warts.<sup>85-89</sup> This treatment for warts is currently more widely used in the United Kingdom where non-prescription 95% silver nitrate caustic applicator pencils are available.<sup>90</sup> In the United States, however, the Food and Drug Administration has warned consumers that "all over-the-counter (OTC) drug products containing colloidal silver ingredients or silver salts for internal or external use are not generally recognized as safe and effective and are misbranded."<sup>91</sup> Clinical application should be done with caution to avoid excessive burns and irreversible tissue staining. Clinical efficacy is moderate. Clearance was achieved in 43% with improvement in an additional 26% after 1 month by application of silver nitrate three times over 9 days. Placebo treatment resulted in 11% clearance and 14% improvement.<sup>92</sup>

#### *Salicylic Acid*

Salicylic acid is a first-line therapy that many patients choose, since it is available over the counter. It is a keratolytic therapy with a mechanism of action that slowly destroys virus-infected epidermis and may cause an immune response from the mild irritation caused by the salicylic acid.<sup>20</sup> It is prepared in concentrations from 10% to 60%.<sup>93</sup> Over-the-counter preparations are available as 17% salicylic acid combined in a base of flexible collodion or as a 40% salicylic acid plaster patch.<sup>94</sup> The advantages of over-the-counter salicylic acid include convenience, minimal expense, negligible pain and reasonable effectiveness.<sup>22,23</sup> Disadvantages are that results require weeks to months of treatment, and the patient must strictly adhere to instructions.<sup>22,23</sup> Side effects can include occasional contact dermatitis due to colophony in the collodion base.<sup>1,95</sup> There is also a potential risk of systemic toxicity in children that can be avoided if lower concentrations or limited areas of treatment are used.<sup>1</sup>

Patient compliance with salicylic acid treatment is extremely important. The wart(s) should be soaked in warm water for 5 minutes before debridement of the dead, hyperkeratotic tissue with an emery board or pumice stone. The salicylic acid preparation should then be applied to the debrided wart.<sup>93</sup> Salicylic acid liquid should be applied every day, and patches must be reapplied every 48 hours.<sup>22,23</sup> Acids are particularly well suited for use in children, but precautions should be taken to prevent them from putting the treated area in their mouths. Acids are also appropriate for plantar warts and sensitive body parts where cryotherapy would be painful.<sup>22,23</sup> Salicylic acid has been applied to plantar warts with some success via iontophoresis.<sup>77,96</sup>

Gibbs et al<sup>19</sup> reviewed 13 trials that assessed topical salicylic acid in concentrations from 15% to 60% with most trials using 15% to 26% with or without lactic acid. Data pooled from six placebo-controlled trials demonstrated a cure rate of 75% (144 of 191) in the salicylic acid treatment arm

compared with 48% (89 of 185) in the placebo arm (odds ratio 3.91, 95% confidence interval 2.40 to 6.36).<sup>19</sup> Monotherapy with 5-fluorouracil, glutaraldehyde, benzalkonium, cryotherapy or podophyllin proved no more effective than salicylic acid-containing paints. Plantar warts may be more amenable to treatment with salicylic acid with occlusion than hand warts.<sup>97</sup> Wart paints should not be used to treat facial warts because of severe irritation and a potential for scarring.<sup>20</sup>

#### *Cantharidin*

Cantharidin is derived from the blister beetle, *Cantharis vesicatoria*.<sup>83</sup> It causes epidermal cell death, acantholysis, and clinical blister formation by interacting with mitochondria.<sup>93</sup> Since 1992, the drug is no longer available in the United States but can be purchased in Canada.<sup>93</sup> Cantharidin should be applied to the pared wart and covered with a nonporous occlusive tape for 24 hours. A blister will form and heal in 1 to 2 weeks.<sup>83</sup> This process should be repeated in 1 to 3 weeks.<sup>93</sup> Cure rates have been reported to be as high as 80% for common, plantar and periungual warts.<sup>93</sup> There is no pain from application of cantharidin. It does not usually cause scarring, although blister formation can be painful and an annular ring may occur around the treated wart.<sup>93</sup> There have been no randomized, controlled trials to test the efficacy of cantharidin for the treatment of nongenital warts.

#### *Cryotherapy*

Cryotherapy is available for the treatment of verruca vulgaris in primary care and dermatology offices. It is considered a second-line therapy.<sup>1</sup> The most commonly used cryogen is liquid nitrogen with a temperature of -196°C.<sup>20</sup> The effect on wart clearance may be through necrotic destruction of HPV-infected keratinocytes or by inducing local inflammation that triggers an effective cell-mediated response.<sup>20</sup> HPV can itself survive and be stored in liquid nitrogen for research purposes; thus, the treatment does not kill the virus, and one should exercise precautions against both the spread of virus from patient to patient by contaminated cryoprobes or swabs and the contamination of liquid nitrogen reservoirs.<sup>98</sup> Verruca-Freeze (CryoSurgery, Inc., Nashville, TN) or equivalents are now available over the counter; however, they only freeze tissue to -70°C and do not freeze tissue as fast as liquid nitrogen.<sup>22,23</sup> Adverse effects with cryotherapy can include hypopigmentation or hyperpigmentation (especially in dark skin), tendon and/or nerve damage when therapy is too aggressive, and annular recurrence around the treated wart if blistering is excessive.<sup>1</sup> Patients with poor circulation should also be treated with caution.<sup>20</sup>

Cryotherapy techniques can vary in application mode, freeze times and intervals between treatments. Liquid nitrogen cryotherapy can be performed with a spray gun or cotton wool bud. Wart cure rates after 3 months with treatments every 2 weeks have been reported to be 47% for cotton wool bud and 44% for spray gun; this difference is not significant.<sup>93</sup> Warts

present for 6 months or less had a greater chance of clearing (84%) within the 3 months compared with warts present for more than 6 months (39%).<sup>93</sup>

Freeze times for warts are defined as traditional or aggressive. Traditionally, cryotherapy is applied until the wart has a 2 mm white halo around it.<sup>1</sup> An aggressive or longer freeze maintains a white halo for 5-20 seconds.<sup>1</sup> In a comparison of traditional freeze versus 10 second freeze, the longer freeze was more effective than the traditional method, although the incidence of pain and blistering is significantly greater.<sup>99</sup>

In a study of a double freeze-thaw technique versus a single freeze technique, it was found that there was no significant difference for cure rates at 3 months in using either technique for hand warts, but the double freeze-thaw technique may have been more effective for plantar warts.<sup>100</sup> Even with paring, callus formation over warts may serve as a thermal insulator and reduce the effect of cryotherapy to below that required to induce even minimal cell damage.<sup>100</sup>

In a study of the frequency of wart cryotherapy and the efficacy of cure at 1, 2 or 3 week intervals, the percentage cured was related to the number of treatments but was independent of the interval between treatments.<sup>101</sup> Optimal treatment may be every 2 weeks, as it achieves a faster cure without affecting department workload, especially for patients who may desire a quicker cure before a forthcoming event.<sup>101</sup>

In an assessment of 16 cryotherapy trials, most compared different regimens instead of comparing cryotherapy to other treatments or placebo.<sup>18</sup> There was no significant difference between cryotherapy versus other treatments or placebo in pooled data of two small trials.<sup>18</sup> More recently, it was demonstrated that there was no significant difference in wart clearance at 3 to 6 months between cryotherapy (65%) and salicylic acid (62%).<sup>102</sup>

An aggressive cryotherapy (10 second) was significantly more effective (52% cure rate) than gentle cryotherapy (brief freeze) (31% cure rate) when data from four trials were pooled.<sup>19</sup> However, pain and blistering occurred in 64 of 100 (64%) participants treated with the aggressive regimen compared with 44 of 100 (44%) treated with the gentle regimen.<sup>19</sup> The optimum number of treatments for warts on the hands and feet in a large population of adults and children was examined by only one trial that demonstrated no significant benefit to prolonging cryotherapy after 3 months (about four freeze treatments).<sup>19</sup>

The optimum treatment interval was examined in three trials. Long-term cure rates comparing 2, 3 and 4 week intervals were not significantly different.<sup>19</sup> The frequency of pain and blistering was higher with shorter treatment intervals, but this may have been due to seeing participants sooner after treatment.<sup>19</sup>

While most of these studies report moderate success, in the hands of some practitioners cryosurgery has been reported to be much more effective. Using local or regional anesthesia prior to treatment, aggressive surgical debulking followed by double freeze-thaw open spray cryosurgery resulted in an 83.5% complete clearance rate with a single treatment in a series of 514 plantar warts. The complete clearance rate rose to 92.5% when those treated two and three times were included.<sup>76</sup> While this was a non-randomized, non-controlled series, the success rate is nonetheless impressive and may speak to the importance of the technique. Overall, evidence concerning the relative merits of cryotherapy compared with placebo and other simpler and safer treatments is inconclusive.<sup>19</sup>

#### *Hot Water*

Simple sequential treatment by immersion in hot water (45°C to 48°C) has been reported to dramatically improve certain cases of cutaneous warts of the hands and feet.<sup>103,104</sup>

#### *Exothermic Patches*

Small patches containing chemicals that produce heat through oxidation upon exposure to air have been applied to warts with anecdotal success.<sup>105</sup>

#### *Ultrasound Hyperthermia*

Several early reports attempted to use ultrasonic therapy to locally heat warts with some success, but this treatment seems to have been largely abandoned.<sup>106-112</sup>

#### *Radiofrequency Ablation*

Localized heating with radiofrequency heat generators as well as surgical excision with radiofrequency electrosurgical knives have been used with moderate success.<sup>113,114</sup>

#### *Microwave Treatment*

*In vitro* treatment of excised warts by applying microwave energy has been shown to produce more HPV DNA damage than CO<sub>2</sub> laser treatment, but there has been no reported clinical application of microwave treatment.<sup>115</sup>

#### *Infrared Coagulation*

Direct application of infrared contact coagulators has been reported as a cheaper, safer and more easily handled alternative to CO<sub>2</sub> laser treatment. The instrument allows adjustable tissue necrosis without tissue adhesion and has yielded remissions with a 10.8% recurrence rate.<sup>116</sup> In comparison to electrocoagulation, infrared coagulation produces similar outcomes.<sup>117</sup>

#### *Carbon Dioxide (CO<sub>2</sub>) Laser*

The CO<sub>2</sub> lasers emit infrared light (10,600 nm) that is absorbed by water. Nonselective thermal tissue destruction results. A focused CO<sub>2</sub> laser beam can be used as a scalpel to excise the wart down to the subcutaneous tissue after which the base of the wart is vaporized by a defocused beam until a clean surgical field is obtained.<sup>118</sup> Two case series described

a 64% to 71% cure rate at 12 months.<sup>20</sup> No randomized, controlled trials have been published on the efficacy of CO<sub>2</sub> laser.<sup>102</sup> Lost skin heals by secondary intention.<sup>114</sup> This treatment may be useful for periungual and subungual warts that are recalcitrant to other treatments.<sup>20</sup> It has also been found to be useful in immunosuppressed patients;<sup>119</sup> however, four cases of hypertrophic scarring following CO<sub>2</sub> laser treatment of plantar warts in cyclosporin-treated renal transplant patients have been reported.<sup>120</sup> Adverse effects of this treatment in immunocompetent patients include postoperative pain, prolonged healing time, and scarring.<sup>83</sup>

In using any laser, hazards may be associated with the laser plume, including pulmonary and infectious hazards from released bacterial, fungal or viral organisms. HPV DNA has been demonstrated in CO<sub>2</sub> laser vapor, as well as in the vapors from electrocoagulation.<sup>121-125</sup>

#### *Erbium:Yttrium/Aluminum/Garnet (Er:YAG) Laser*

The Er:YAG laser emits a shorter wavelength infrared radiation (2940 nm) that is absorbed 12 to 18 times more efficiently by water-containing superficial cutaneous tissues than is the 10,600 nm wavelengths emitted by the CO<sub>2</sub> laser.<sup>126</sup> The Er:YAG laser has a smaller zone of thermal damage, thereby allowing more precise thermal ablation with minimal scarring. Warts in a variety of locations have been successfully eliminated in 75% of patients after a single treatment, with a 25% relapse rate within 1 year after treatment.<sup>127</sup> Approximately 14% of patients are non-responders.<sup>128</sup> Postoperative healing occurred after 7 to 10 days, but erythema that occurred in all patients required 2 months to subside. A potential safety feature of this laser is that HPV DNA has not been detected in the laser plume.<sup>129</sup>

#### *Neodymium:YAG (Nd:YAG) Laser*

The Nd:YAG laser's principal emission wavelength is at 1064 nm, still in the infrared range. Hyperthermic treatment with this laser has been reported to cause remission with no recurrence in several case reports and case series.<sup>130,131</sup> In biopsied tissues, pre- and post-treatment with either cryotherapy or Nd:YAG hyperthermic therapy, HPV DNA was reduced from 100% to 96% after cryotherapy and from 100% to 0% after laser treatment.<sup>132</sup> Nd:YAG laser light has been guided through fiberoptics in a flexible probe to successfully treat recurrent respiratory papillomatosis caused by HPV 6 and 11 in children. By combining this probe with a suction channel to remove smoke and pyrolysis products, an optimal field of view is maintained and a minimal load of potential infectious laser plume and toxic pyrolysis products is removed during the procedure.<sup>133</sup> Nd:YAG lasers are also utilized in therapeutic treatment of genital tract lesions and for cervical conization of early neoplasias involving HPV infections.<sup>134,135</sup>

#### *Pulsed Dye Laser*

The mechanism of action of the pulsed dye laser is through selective microvascular destruction of dilated capillaries in

the warts. This happens as a result of thermal damage occurring upon yellow light absorption (585 nm) by oxyhemoglobin. Thermal damage, removal of the blood supply, and a cell-mediated immune response are believed to contribute to wart healing.<sup>114</sup> The treatment sensation has been compared to being snapped by a rubber band and is considered relatively painless.<sup>55</sup> However, some patients do report severe intraoperative pain.<sup>136,137</sup> As the vessels burst, purpura develops within minutes in the treated areas and takes 10 to 14 days to resolve as macrophages digest the residues.<sup>137</sup> Pulsed dye laser causes minimal postoperative pain and completely heals in 2 to 4 weeks.<sup>114</sup> It produces less pain and scarring than with CO<sub>2</sub> laser treatment and has been used for facial warts and perianal warts in children.<sup>20,138,139</sup>

Pulse dye laser has been reported to result in complete remission in 48% to 95% of cases.<sup>102,137,140-147</sup> One study found no statistically significant difference among cure rates between pulsed dye laser (66%) compared to conventional cryotherapy or cantharidin therapy (70%).<sup>147</sup> It appears that warts in nonacral locations respond better than those on the hands, and plantar warts respond the least to this treatment.<sup>137,147</sup>

#### *Potassium-Titanyl-Phosphate (KTP) Laser*

The KTP laser has been utilized in the treatment of recalcitrant cutaneous warts and when treated to complete clearance, no recurrence occurred.<sup>148</sup>

#### *Photodynamic Therapy*

Rather than using endogenous target absorbers (i.e., water for the CO<sub>2</sub> laser and oxyhemoglobin for the 585 nm pulsed dye laser), photodynamic therapy uses light of a wavelength absorbed by specific photosensitizing molecules that are exogenously administered to the target tissue.<sup>149</sup> One agent commonly used is 5-aminolaevulinic acid (ALA), which is a prodrug that stimulates porphyrin accumulation in the tissue.<sup>150,151</sup> Porphyrins then act as the photosensitizing agent. When illuminated, the porphyrins induce a photooxidation cascade that damages the involved cells. The lights used range from lasers to photoemitting diodes to white lights that cover the porphyrin excitation peak. The ALA is applied topically as an ointment or cream and preferentially accumulates in the lesions.<sup>152</sup>

Photodynamic therapy has been applied to warts in sensitive mucosal tissues including venereal warts and cervical intraepithelial neoplasia (CIN) in the vulva, penis and urethra and to oral and respiratory tract papillomas.<sup>51,152-155</sup> Generally, results are equivalent to or superior to other treatment modalities with the advantage that little, if any, scarring results. Additionally, the photosensitizers fluoresce which can assist in the pretreatment localization of lesions.<sup>8,156</sup>

Photodynamic therapy has also been used to treat common warts on the hand, flat warts and plantar warts.<sup>157-160</sup> In the

treatment of plantar warts, delivery of the ALA is performed after keratolysis with urea and salicylic acid and gentle curettage.<sup>161</sup>

#### **Virucidal Therapy**

##### *Glutaraldehyde*

Glutaraldehyde is virucidal and available as a 10% water miscible gel or alcohol solution.<sup>1</sup> Application of glutaraldehyde is typically applied twice a day and can stain the skin brown, as well as cause contact sensitivity.<sup>1</sup> Treatment has been reported to be as effective as with salicylic acid with cure rates over 70%.<sup>1</sup> No randomized, controlled trials for glutaraldehyde treatment of warts have been published.<sup>19</sup>

##### *Formaldehyde*

Formaldehyde is also virucidal and works by disrupting the upper layer of epidermal cells and possibly damaging the virions.<sup>1</sup> Available 0.7% gels or 3% solutions are used to soak plantar warts to speed resolution.<sup>20</sup> Formaldehyde, widely used as a preservative in many products such as lotions and shampoos, can cause sensitization and should be avoided in patients with eczema and allergies.<sup>1</sup>

One controlled trial of formaldehyde wart treatment involved 192 participants with plantar warts. Cure rates ranged between 61% and 67% at 2 months but were not significantly different between the four treatment groups: 3% formalin, 3% formalin with paring, water (placebo) and sucrose tablets (placebo).<sup>19</sup>

##### *Formic Acid*

Formic acid is the chemical irritant found in the stings and bites of many hymenopteran insects, including bees and ants, and was first isolated from red ants, hence the name from the Latin for ant, formica. It is also the irritant in the leaves of stinging nettles. In a nonrandomized, placebo-controlled, open trial in 100 patients, a topical 85% formic acid/needle puncture technique resulted in a 92% complete clearance rate as compared with 6% in the placebo (water) group.<sup>162</sup> The mechanism of action of this agent is not known. It may relate to the mode by which formaldehyde acts, or it may act in the series of caustic acids. With salicylic acid being the weakest, trichloroacetic acid being of medium strength, and bichloroacetic acid being the strongest, the strength of formic acid lies between that of salicylic acid and trichloroacetic acid.

##### *Antiviral Drugs*

Cidofovir is a nucleoside analogue of deoxycytidine monophosphate that inhibits DNA synthesis, induces DNA fragmentation, reduces epithelialization and enhances excoriation.<sup>163-165</sup> It has been used successfully in HIV-positive patients for the topical treatment of genital warts.<sup>166-170</sup>

A case has been reported in which a homosexual man with HIV had multiple extensive warts. When treated with oral antiretroviral therapy (didanosine, stavudine and efavirenz or abacavir), there was a nearly total regression of the viral warts

along with a significant improvement in the patient's immune status.<sup>171</sup>

## Antimitotic Therapy

### *Bleomycin*

Bleomycin, an antibiotic derived from *Streptomyces verticillus*, is reserved for recalcitrant warts that have failed other types of treatment.<sup>20</sup> It selectively affects squamous cell and reticuloendothelial tissue.<sup>172</sup> DNA and protein synthesis are inhibited, and apoptosis is triggered. Bleomycin is not thought to bind directly to HPV.<sup>93</sup> Bleomycin causes acute tissue necrosis that may stimulate an immune response, as evidenced by the fact that it is less effective as a wart treatment in immunosuppressed renal transplant patients.<sup>22,23,173,174</sup> Bleomycin treatment of warts results in significant systemic drug exposure and should not be used on pregnant women, children, immunosuppressed patients or patients with vascular disease.<sup>93,174</sup> Adverse effects include injection pain and burning, erythema, swelling and pain within 24 to 72 hours after injection before a black thrombotic eschar forms. Raynaud's phenomenon is a definite concern in treated digits, and the nail may become dystrophic or be completely lost.<sup>93,175,176</sup> Bleomycin may also cause lymphangitis and flagellate hyperpigmentation.<sup>1,177</sup>

A double-blind, placebo-controlled study of warts recalcitrant twice to conventional treatments compared one to two intralesional injections of bleomycin to injections of normal saline. Plantar warts (60%), periungual warts (94%) and warts elsewhere on the extremities (95%) were cleared.<sup>178</sup> The success of bleomycin treatment can be technique-dependent.<sup>179</sup> Using a bifurcated needle has been reported to improve outcome.<sup>180,181</sup> One study achieved a 92% cure rate of 258 warts with only one treatment of bleomycin using a technique of multiple wart punctures with a bifurcated needle.<sup>180</sup> The bifurcated needle puncture technique required 0.001 units of bleomycin compared to 0.2 units injected intralesionally under the base of a wart. Only the soft epidermis comes in contact with the bleomycin avoiding dermal exposure.<sup>180</sup> Another technique is to apply the bleomycin solution by drops onto the wart and then prick the solution into the wart using a 28-gauge lancet needle. This has resulted in a 92% clearance rate.<sup>182</sup> Others have used modified tattooing devices with some success.<sup>172</sup>

Five randomized, controlled trials have evaluated the effectiveness of bleomycin;<sup>102</sup> however, it is difficult to compare the trials.<sup>19</sup> Cure rates ranged from 16% to 94%. Three trials demonstrated 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. Different concentrations of bleomycin also made no significant difference after 3 months.<sup>102</sup>

### *Retinoids*

Epidermal growth and differentiation are disrupted by retinoids, so wart growth is affected. Retinoids are also potent immunomodulators.<sup>183</sup> There is some evidence that retinoids

can downregulate HPV transcription in affected cells as well.<sup>184,185</sup> Retinoids can be administered topically or systemically. Treatment of warts with a tretinoin cream resulted in 85% clearance in a series of children as compared to 32% spontaneous clearance in controls.<sup>186</sup> Eighty percent of children treated with daily etretinate orally for up to 3 months exhibited complete regression, with the remainder showing partial regression.<sup>187</sup> Other trials and case reports have shown systemic retinoids, especially synthetic isotretinoin, to have an effect on a variety of warts, particularly genital warts.<sup>188-191</sup> A great deal of interest has been expressed in the use of retinoids as a potential chemopreventive and/or therapy in HPV-related cervical cancer.<sup>192</sup>

### *Podophyllin*

The rhizomes of the mayapple plant (*Podophyllum peltatum*) that grows throughout eastern and midwestern North America are the source of podophyllin resin, the crude alcohol extract containing podophyllotoxin, 4-demethylpodophyllotoxin,  $\alpha$ -peltatin and  $\beta$ -peltatin.<sup>193</sup> The Penobscot Indians of the northeastern United States used poultices of mayapple for the treatment of warts.<sup>194</sup> Physicians in New Orleans used podophyllin for the treatment of genital warts in the 1930s.<sup>195,196</sup>

Podophyllin resin has been used mostly in the treatment of anogenital warts. A 1990 study demonstrated a 41% complete clearance rate for patients who received up to six weekly treatments for external genital warts, but only a 17% clearance at 3 months.<sup>197</sup> Similarly, a 1991 study demonstrated a 45% clearance rate of anogenital warts at 3 months with 73% remaining clear at 9 months. This outcome was compared to a 23% clearance rate with subcutaneous interferon- $\alpha_{2a}$  at 3 months with 77% remaining clear at 9 months.<sup>198</sup> An advantage to podophyllin treatment is that it can be self-administered with greater patient convenience and cost effectiveness.<sup>199</sup>

In studies conducted between 1969 and 1975, podophyllin treatment was shown to have an 81% cure rate for simple plantar warts (comparable to an 84% cure rate for a paint containing salicylic and lactic acids).<sup>97</sup>

Guidelines of the United States and the United Kingdom on the treatment of anogenital warts include podophyllin in their recommendations,<sup>20,27,29</sup> but it has been shown that podophyllin resin is both less effective and less cost effective than purified podophyllotoxin, the active ingredient, and there is no evidence that podophyllin in combination with any other agent enhances clinical response.<sup>200-205</sup> In addition, podophyllin preparations vary between batches and have been shown to have toxic side effects.<sup>203,204,206</sup> In contrast, purified podophyllotoxin exhibits low clinical toxicity.<sup>204,205</sup>

### *Podophyllotoxin*

*Podophyllum hexandrum* grows in the mountainous regions of India and contains a higher content of podophyllotoxin, the active component.<sup>207</sup> Podophyllotoxin binds to microtubules and causes mitotic arrest in the metaphase of cell division.<sup>208</sup> In a small (19 treatment, 19 control), double-blind, randomized clinical trial of self-administered podophyllotoxin solution versus vehicle in the treatment of genital warts, patients were instructed to administer 0.5% solution or vehicle at home twice daily for 3 consecutive days of each week for 4 weeks.<sup>209</sup> At the end of the 4 week regimen, the treatment group experienced a 94.9% reduction in wart area and 84.1% reduction in wart count as opposed to 7.1% and 2.6% for the vehicle only placebo. This translates into 1.1 patients needed to treat before seeing a significant reduction in wart area due to treatment, and 1.2 patients for wart count. These are very impressive needed to treats; however, only 21% of patients remained free of warts 2 weeks after treatment, and all patients available for long-term follow-up experienced recurrences. Thus, the podophyllotoxin solution appears highly effective for short-term treatment of symptoms but does not provide a long-term cure.

In a more recent randomized comparison of external genital wart treatment with a weekly application of 20% podophyllin solution versus self-administered 0.5% podophyllotoxin cream twice daily for 3 days in weekly intervals, the total eradication of warts was 74% versus 94% respectively.<sup>210</sup> The advantage of easy self-application of the podophyllotoxin cream makes this an appealing alternative for the treatment of external genital warts.

### **Immunotherapy**

#### *Oral Zinc Sulphate*

Dietary zinc has profound effects on the human immune system, and deficiency leads to reduced immune capacity.<sup>211,212</sup> Based on this, a placebo-controlled clinical trial was attempted using oral zinc sulphate (10 mg/kg daily) to treat recalcitrant warts. Complete clearance was reported in 87% of the treatment group versus no clearance in the placebo group.<sup>213</sup>

#### *Contact Sensitizers*

The mechanism of action for topical immunotherapy with contact sensitizers is proposed to be a type IV hypersensitivity reaction.<sup>1</sup> The immune response is purported to be directed against a complex of contact agent hapten bound to protein of viral or human origin that enhances wart regression.<sup>1</sup> An effective topical immunotherapy contact sensitizer should ideally be readily available, able to sensitize at least 95% of the normal population, chemically stable, economical, free of significant adverse effects and rarely occurring in the human environment.<sup>214</sup>

In 1973, Lewis first reported immunotherapy using dinitrochlorobenzene (DNCB) for common warts.<sup>215</sup> Two randomized, controlled trials have compared DNCB to placebo with results demonstrating 80% clearance of warts

with DNCB and 38% clearance with placebo.<sup>56,102</sup> DNCB is mutagenic, so it is no longer used in clinical settings.<sup>215</sup>

Diphencyprone (DCP), the standard sensitizer used for topical immunotherapy, is nonmutagenic and is available in acetone solution.<sup>215</sup> It has a shelf life of 3-6 months at room temperature if stored in an amber glass bottle to prevent light degradation.<sup>215</sup> Another nonmutagenic contact sensitizer, squaric acid dibutyl ester (SADBE), has been used in treatment of recalcitrant warts. SADBE is more expensive and less stable in solution than DCP.<sup>214,215</sup>

Buckley et al reviewed resistant hand and foot warts treated with DCP over 8 years.<sup>216</sup> Patients were sensitized with a 2% DCP solution on the medial upper arm every 10 to 14 days until local erythema and vesiculation occurred. Treatment was repeated up to 3 times. Pared warts were then treated with stepwise concentrations of DCP: 0.01%, 0.05%, 0.1%, 0.25%, 0.5%, 1.0%, 1.5%, 2.0%, 3.0%, 4.0% and 6.0%. Plantar warts were treated with 2.0% and digital warts with 0.1% as initial concentrations. Treatments were applied every 1 to 4 weeks, and the DCP concentration was adjusted by the patient's response. At each visit, after questioning about adverse effects and degree of improvement, the concentration of DCP was increased by one step if there was no response. It was kept constant if there was an adequate response and was lowered by one step if severe blistering occurred. Forty-two of 48 individuals completed treatment and exhibited an 88% clearance rate. Adverse effects occurred in 56% of the 48 patients and included painful blistering near the wart, blistering at the sensitization site, pompholyx-like or more generalized eczematous eruption, influenza-like symptoms, vesiculation elsewhere due to passive transfer of DCP and inguinal adenopathy.

Patients with recalcitrant plantar, palmar, periungual and digital warts are candidates for DCP treatment.<sup>214</sup> Compared to other treatments, DCP is less destructive, less costly, less time-consuming to perform, and can be used for the concurrent treatment of multiple warts.<sup>214</sup> However, treatment should be limited to the clinical setting, and patients need sequential applications to ensure maximal outcome.<sup>214</sup>

#### *Intralesional Injection of Interferon*

For genital warts that are recurrent or recalcitrant to other treatments, intralesional injection of interferon- $\alpha$  has been tested in a randomized, double-blind, placebo-controlled, multicenter trial. Leukocytic interferon can both kill viruses and stimulate the immune system. The interferon or placebo was injected twice weekly for up to 8 weeks. Complete clearance was seen in 62% of interferon- $\alpha$  patients compared to 21% of placebo-treated patients.<sup>217</sup> Intralesional interferon- $\alpha$  has also been used successfully in the treatment of recurrent oral warts in AIDS patients.<sup>218</sup>

#### *Intralesional Injection of Mumps or Candida Antigen*

Intralesional injection of mumps or *Candida* may be a

treatment option for recalcitrant warts that have not resolved with other therapies. One trial compared the intralesional injection of one wart with *Candida* or mumps antigen to cryotherapy of all warts.<sup>219</sup> Excluded were patients with prior allergic response to mumps or *Candida* antisera, pregnancy, HIV infection, iatrogenic immunosuppression, primary immunosuppression or any generalized dermatitis. An intradermal injection of 0.1 ml of mumps and *Candida* antigen was placed in the right and left forearms, respectively. The amount of reaction was read after 48 to 72 hours. Based on the size of test reaction, the responder's largest wart was treated with an intralesional injection of mumps or *Candida*. Nonresponders and randomized immune responders received cryotherapy with a 1- to 2-mm halo of frozen tissue for 30 seconds using a double freeze-thaw technique. Treatments with cryotherapy and intralesional antigen injection were performed every 3 weeks until the warts completely cleared or for a total of three treatments. On follow-up, the response to the treatment (decrease in wart number and size) was assessed.

Of 115 patients, 30% were anergic to *Candida* and mumps antigen, and 70% had immunity to at least one of the antigens. The immune group was divided into 32% receiving cryotherapy, 56% receiving intralesional mumps antigen and 12% receiving intralesional *Candida* antigen. The anergic group included 82% of patients receiving cryotherapy and 18% who refused treatment. Complete wart clearance was achieved in 74% of immune individuals treated with mumps or *Candida* antigen immunotherapy compared to 55% treated with cryotherapy. Anergic patients treated with cryotherapy exhibited 58% clearance. Seventy-eight percent of patients treated with *Candida* and mumps antigen immunotherapy had resolution of untreated warts in different anatomical locations. Six patients developed flu-like symptoms (fever, malaise and myalgia) within 12 hours of intralesional injection of antigen that lasted up to 24 hours. Symptoms were treated with nonsteroidal anti-inflammatories. The most common complaints were pain upon intralesional injection and pruritus within the first 24 hours.

It was concluded that immunotherapy should serve as first-line treatment for immune individuals with numerous (>5) or large (>1 cm) warts and as an effective second-line treatment in immune individuals who are judged to have failed cryotherapy.<sup>219</sup> The mechanism of action for this type of immunotherapy was proposed to be based on trauma and subsequent inflammatory reaction of the intralesional injection leading to an HPV-directed immunologic reaction.<sup>219,220</sup>

Another trial used the same method to assess immunotherapy by intralesional mumps or *Candida* antigens for recalcitrant warts in children who had previously been treated with liquid nitrogen and at least one other type of treatment.<sup>44</sup> Children in the study (n=47) each had an average of 5.96 warts. Complete clearance was achieved in 47% of treated warts

with an average of 3.78 treatments. Greater than 25% improvement of warts was seen in an additional 34% of the children treated. Sixty-eight (68%) with multiple warts noted at least partial resolution of anatomically distinct, untreated warts. Fourteen children experienced 100% resolution of distant warts. Side effects included itching at the injection site in 50% of the children and 10% had edema or erythema.<sup>44</sup> None reported severe pain or scarring. The initial skin test induration size of mumps and *Candida* antigen did not affect the clearance of the treated wart or distant wart resolution.

The lower response rate compared to the former study was thought to be due to the inclusion of only children with recalcitrant warts. Higher response rates may be expected in the initial treatment of children's warts. There may also be less immune response to skin test antigens in children as compared to adults. It was proposed that intralesional injection of mumps or *Candida* antigen be considered a first-line therapy in children with large or multiple warts and a second-line therapy in warts recalcitrant to standard therapies, particularly because of its high level of tolerability.<sup>44</sup> A variety of adverse reactions, including delayed-type hypersensitivity reaction, has been reported with *Candida* antigen treatments.<sup>221</sup>

#### *5-Fluorouracil (5-FU)*

Fluorouracil has been used topically as an antiproliferative agent for warts.<sup>18,19</sup> In one prospective placebo-controlled, single-blind, randomized trial, up to 70% of warts underwent complete response when treated with 5-FU combined with lidocaine to reduce pain and epinephrine to induce vasoconstriction in order to sustain high local drug concentrations.<sup>222</sup>

#### *Cimetidine*

Daily doses of 20 to 40 mg/kg cimetidine, an H<sub>2</sub>-receptor antagonist, cleared up to 82% of recalcitrant warts in open label studies.<sup>223</sup> Cimetidine is postulated to act as an immunomodulating agent at high doses by inhibiting suppressor T-cell function while increasing lymphocyte proliferation, thereby enhancing cell-mediated immune responses.<sup>223,224</sup> Others found insufficient evidence of efficacy in three small randomized, controlled trials between cimetidine and placebo.<sup>102</sup>

In a randomized, placebo-controlled, double-blind study of treating recalcitrant warts in adults with a 12 week course of cimetidine at 2400 mg/day (22-46 mg/kg daily) or placebo, the clearance rate of warts with cimetidine and placebo was 26% and 5%, respectively (not significant;  $P = 0.085$ ).<sup>223</sup>

Another double-blind, placebo-controlled study compared 12 weeks of treatment with cimetidine at 400 mg 3 times per day versus placebo in patients over 12-years-old.<sup>225</sup> Wart clearance for the cimetidine group was 27% and 22% for placebo, which was not a statistically significant difference. The study investigators proposed a placebo effect for cimetidine.

A third randomized, controlled trial used cimetidine in doses of 25 to 40 mg/kg daily versus placebo in women and children ages 4 to 39 years old.<sup>226</sup> The cure rate of warts was 32% with cimetidine and 30.9% in the placebo group, again not a statistically significant difference.

By contrast, in a retrospective assessment of 216 patients who were administered oral cimetidine therapy for verrucae plantaris, it was concluded that cimetidine is a safe, effective lone treatment modality for verrucae in all age groups.<sup>227</sup>

#### *Levamisole*

Levamisole is another immunomodulating drug that has been used effectively in the treatment of flat and common warts with moderate success.<sup>228</sup>

#### *Imiquimod*

Imiquimod 5% cream is an immunomodulator that may stimulate cytokines, including interferon- $\alpha$ , interleukin-1, interleukin-6, tumor necrosis factor- $\alpha$ , granulocyte-macrophage colony-stimulating factor and granulocyte colony-stimulating factor.<sup>83</sup> Absorption of imiquimod through intact skin is minimal.<sup>1</sup> Its use in the treatment of external anogenital warts was approved by the United States Federal Drug Administration in 1997, and it has more recently been approved for the treatment of nonhyperkeratotic, nonhypertrophic actinic keratoses and superficial basal cell carcinomas.

The use of imiquimod for the treatment of non-genital warts has not been formally assessed by a randomized, controlled trial. However, in an open label, uncontrolled study using imiquimod 5% cream to treat common cutaneous warts, patients applied imiquimod 5% cream to the warts once a day for five successive days in a week and washed it off in the morning with soap and water.<sup>229</sup> The patients continued this regimen for up to 16 weeks or until the warts were no longer visible. Total clearance of warts occurred in 30% of patients; 26% of patients had a >50% reduction in wart size. A breakdown of wart clearance by location included trunk (75%), face (70%), hands (60%), and feet (37.5%). Follow-up was performed at 32 weeks, at which time no warts had recurred in the treated areas. An adverse local inflammatory reaction was reported in 31% of patients, but it was considered mild and transient. Other side effects were erosions, pruritus, bacterial infection, fever and scarring. Disadvantages of using imiquimod 5% cream were the high cost and the length of average treatment (9.5 weeks). Others have reported effective treatment of recalcitrant plantar, periungual and subungual, as well as anogenital warts by applying imiquimod cream over 12 weeks with no evident recurrence or side effects.<sup>230-235</sup> Application of imiquimod cream following laser treatment of anogenital warts, beginning when wound healing had completed, proved effective in reducing recurrences.<sup>236</sup> Advantages of using imiquimod 5% cream in children included less pain and trauma than other treatments, such as salicylic acid, cryotherapy or laser.<sup>229</sup> Among adults, the costs and pain of

office-based procedures can be avoided when the imiquimod cream is self-applied.<sup>237</sup>

#### *Bacillus Calmette-Guérin Therapy*

Intravesical instillation of viable bacillus Calmette-Guérin is a standard adjuvant treatment for recurrent superficial bladder cancer.<sup>238</sup> The mode of action is based on stimulation of the local immune response.<sup>239,240</sup> The immune responses to malignant and virally transformed cells are similar.<sup>241,242</sup> Therefore, topical bacillus Calmette-Guérin treatment has been attempted in the treatment of venereal warts. Complete response has been achieved in 60% to 92% of patients treated after 1 or 2 cycles, and they remained disease free after 6 to 9 months. Eight percent to 30% were unresponsive.<sup>243-245</sup>

#### *Vaccines*

Early attempts at vaccination for the treatment of persistent or recurrent anal and perianal venereal warts utilized an autologous vaccine prepared from wart extracts obtained from individual patients that was injected subcutaneously weekly for six weeks. Excellent results were obtained in 84% of patients with only 5% not responding, and all complete remissions that were followed remained disease free for an average of 46 months.<sup>246</sup>

Today, the development of new strain-specific HPV vaccines against venereal warts is progressing rapidly.<sup>247-252</sup> Clinical trials of vaccines to prevent acquisition of oncogenic HPV are proving to be both safe and effective.<sup>30</sup> Through recombinant genetic engineering techniques, the major viral capsid L1 protein is expressed on the surface of another organism (such as a yeast cell or baculovirus) so that the organism appears like a non-infectious HPV virus-like particle (VLP).<sup>253</sup> The purified recombinant L1 capsid proteins can also self-assemble into highly immunogenic VLPs.<sup>254</sup> VLP vaccines designed to express HPV 11, 16 or 18 L1 protein are highly immunogenic.<sup>255-259</sup> Studies using HPV 16 L1 VLP vaccine to immunize at-risk women have proven effective.<sup>254,260</sup> Seventeen to 18 months after vaccination, none exhibited a cervical intraepithelial neoplasia grade 3 (CIN/3) caused by HPV 16 infection. A bivalent HPV 16, 18 L1 VLP vaccine has proven effective in preventing incident and persistent cervical infections with HPV 16 and HPV 18 and associated cytological abnormalities and lesions.<sup>261</sup> In a randomized, double-blind, placebo-controlled, multicenter, phase II efficacy trial, a quadrivalent HPV (6, 11, 16 and 18) L1 VLP vaccine provided a 90% reduction in the incidence of persistent infection or disease after 36 months as compared to placebo.<sup>36,37</sup> While these vaccines hold great promise for the prevention of nascent viral warts, they are thought less likely to be of therapeutic value.<sup>39</sup>

With the ongoing development of these new vaccines, a variety of questions will need to be addressed before an HPV vaccination program can be started.<sup>262-265</sup> One major hurdle will be to promote an effective universal program to immunize preadolescents (10 to 13-year-olds who are likely

to be HPV negative) with these vaccines<sup>36,266-268</sup> in contrast to vaccination as a part of a HPV screening program in adults.<sup>269-273</sup> Substantial barriers to HPV vaccine acceptance by parents and adolescents will have to be overcome in addition to the common barriers to immunizations in general.<sup>250,274,275</sup> Questions will have to be answered as to whether to promote the vaccine as a cancer preventive or a sexually transmitted disease preventive measure.<sup>276</sup> In addition to education during clinic visits, tailored multi-media campaigns on HPV can be useful.<sup>277</sup> To date, no vaccines have been engineered against the HPV types that cause common warts.

### **Combination Therapies**

Due to the frustrating resilience and recurrence of many wart cases, attempts are commonly made to combine therapies. In a cross-sectional survey of treatment choices for anogenital warts in nine genitourinary medical clinics across the United Kingdom, about 11% of all single treatments involved a combination of two or more agents.<sup>278</sup> Treatment decisions were based upon the number of warts, site, morphology, patient preference for treatment and co-existing medical conditions (e.g., immunodeficiency, pregnancy). It was concluded that there is little evidence to support combination therapy and that more information is needed on complications and efficacy before recommendations can be made. A sample of combination therapy outcomes in other studies follows:

#### *5% Imiquimod + Salicylic Acid*

Plantar warts have been successfully treated using 5% imiquimod cream under occlusion with a 40% salicylic acid pad. It was thought that the salicylic acid facilitated delivery of the imiquimod through the thick skin surface on the plantar surface.<sup>279,280</sup>

#### *Cryotherapy + 5% Imiquimod + Salicylic Acid*

A 50% to 100% clearance rate after 6 to 9 weeks has been reported after treatment with liquid nitrogen cryotherapy followed by 17% salicylic acid at bed time and 5% imiquimod each morning.<sup>281</sup>

#### *5-FU + Salicylic Acid*

In an uncontrolled, retrospective study, twice daily topical application of 5-FU (0.5% or 5.0%) was combined with salicylic acid (17% or 40%) to treat plantar warts with complete clinical resolution in all patients.<sup>282</sup> Recurrence occurred in 15% of lesions, but these subsequently resolved upon repeated treatment.

#### *Systemic Interferon- $\alpha_{2b}$ + Isotretinoin*

In the treatment of venereal warts, statistically significant higher remission rates and lower recurrence rates with shorter treatment durations were achieved with systemic interferon- $\alpha_{2b}$  plus isotretinoin versus the retinoid alone.<sup>283-286</sup> This combination therapy has also been used to successfully treat cases of epidermodysplasia verruciformis, a genetically determined susceptibility to widespread and persistent HPV infection.<sup>287,288</sup>

#### *Intralesional Interferon- $\alpha_{2b}$ + Podophyllin Resin*

In a medium sized (49 combination therapy, 48 monotherapy) randomized trial, patients received either a combination intralesional interferon- $\alpha_{2b}$  ( $1.5 \times 10^6$  IU) plus topical 25% podophyllin resin or topical podophyllin resin alone.<sup>289</sup> Complete clearance of treated warts was seen in 67% of those receiving combination therapy versus 42% in those receiving monotherapy with podophyllin. Maximal response was exhibited after 2 weeks of therapy. Additionally, 18% of warts persisted despite either treatment, and after 11 weeks of follow-up in those who had seen complete clearance, a 67% recurrence occurred in the combination arm, and 65% recurrence was seen in the podophyllin-only arm.

#### *Podophyllin + Vidarabine*

CIN is considered to be the precursor to cervical cancer.<sup>290</sup> The co-application of vidarabine and podophyllin over six treatments resulted in the cytological and histological regression of lesions and the disappearance of HPV 16 and 18 DNA in 17 of 21 (81%) of women with CIN I-II.<sup>291</sup> Vidarabine is a DNA polymerase inhibitor that suppresses HPV gene expression in immortalized human cervical keratinocytes and cervical cancer cell lines *in vitro*.

#### *Cryotherapy + Podophyllotoxin*

In the treatment of anogenital warts in the United Kingdom, a combination of cryotherapy and podophyllotoxin is the most common first line treatment, regardless of site.<sup>278</sup>

#### *Er:YAG + Podophyllotoxin*

Recalcitrant palmoplantar warts have been treated with an ablative Er:YAG laser followed by 0.5% podophyllotoxin solution after wound healing to yield an 88.6% complete response rate with a 5.7% relapse rate.<sup>128</sup>

#### *Pulsed Dye Laser + Intralesional Bleomycin*

A pulsed dye laser has been used to pretreat or "prepare" recalcitrant warts immediately prior to intralesional bleomycin injection to help assure basal drug delivery.<sup>292</sup> This treatment resulted in 100% clearance in immunocompetent patients and 89% clearance in subjects on long-term immunosuppressant drugs.

#### *Photoselective Dye Laser + Photosensitizer for Photodynamic Therapy*

In a sizable comparison trial, 81% (91/112) of warts were cured in an average of 3.34 sessions by photoselective laser destruction using a pulsed dye laser alone. Ninety-six percent (73/76) of warts were cured in 2.54 sessions using photodynamic therapy with aminolevulinic acid-induced protoporphyrin as a photosensitizer,<sup>293</sup> and 100% (86/86) of warts were cured when the therapeutic modalities were combined.<sup>294</sup> Warts in a variety of locations were treated. These cure rates are very promising, but no information on recurrence was provided.

### *Combined Antigen Injection*

Injection of a combination of *Candida albicans*, mumps and *Trichophyton* has been shown to be more effective than and as safe as single antigen injection in the treatment of cutaneous warts.<sup>295</sup>

### *Cimetidine + Levamisole*

It has been reported that a treatment with combined cimetidine and levamisole is approximately twice as effective as cimetidine alone in the treatment of recalcitrant warts.<sup>296,297</sup>

### *Electrocautery + Cidofovir*

In a series of HIV patients with genital warts, surgical treatment by electrocautery resulted in a 93% clearance rate but a 74% relapse rate. Topical 1% cidofovir gel resulted in a 76% clearance rate with a 35% relapse rate. Using electrocautery followed by cidofovir gel application, the clearance rate was 100% with 27% relapse.<sup>298</sup>

### *Antiretroviral Regimen + Protease Inhibitor*

In HIV patients with recalcitrant hand warts, resolution has been observed when antiretroviral nucleoside analogue reverse transcriptase inhibitors [azidothymidine (AZT, zidovudine), dideoxyinosine (ddI, didanosine) dideoxycytidine (ddC, zalcitabine), (-)2',3'-dideoxy, 3'-thiacytidine (3TC, lamivudine), 2',3'-didehydro-3'-deoxythymidine (d4T, stavudine)] or non-nucleoside reverse transcriptase inhibitor (nevirapine, loviride, delavirdine) drug therapies were combined with potent protease inhibitors (i.e., ritonavir, indinavir and/or saquinavir).<sup>299,300</sup> For facial warts in HIV patients, combined reverse transcriptase inhibitors and protease inhibitors have been used in addition to ablative treatment with a pulsed dye laser with good results.<sup>301</sup>

## **Conclusion**

As can be seen, an enormous variety of wart treatment approaches have been attempted. Choosing the best wart treatment from this armamentarium can be difficult. Recalcitrant warts that have been present for over 6 months are more resistant to treatment than warts present for less than 6 months. Remission and recurrence can seem unpredictable. Invasive methods are often painful and require long recovery periods. Topical management is usually dependent on patient compliance and requires long application periods.

High quality randomized, controlled trials upon which to base evidence-based decisions are not available for most treatments, so they are not considered in official treatment guidelines. The highest quality of clinical evidence for monotherapies exists for cryotherapy (A, I), followed by photodynamic therapy (B, I), salicylic acid, bleomycin and retinoids (B, II), formaldehyde (C, II), thermocautery and glutaraldehyde (C, III), chemical cautery, CO<sub>2</sub> laser, pulsed dye laser and topical sensitization (C, IV), and cimetidine (D, I).<sup>27</sup> Official recommendations for treatment vary with site and type of wart.<sup>27</sup> However, review of the literature suggests

much higher success rates with less widely tested approaches and combination therapies.

Future research is needed to find a superior treatment of viral warts. This research should focus on the development of a specific antiviral therapy for HPV. The most exciting and promising treatments that are appearing on the horizon are the type-specific HPV vaccines. While current research is focused on oncogenic HPV, the same technologies could be applied to those HPV types that cause the more benign cutaneous warts. In the meantime, in future studies of verrucae, regardless of treatment approach it is prudent to consider the duration of each lesion, previous types of therapy and wart subtype, and to match patients by age, wart number, subtype and duration.<sup>147</sup>

It is of paramount importance when choosing from the armamentarium of wart treatments that the therapy be tailored to meet the needs of the patient and healthcare provider. In practice, the treatment of warts is likely to require an individualized approach and usually requires more than one therapeutic modality to achieve complete resolution. The management of warts depends on the age of the patient, the site of infection, the size, number and types of warts involved, the patient's immunological status, treatment availability and cost, and the patient's desire for therapy and ability to adhere to the treatment regimen. For children, it is desirable to have an effective and painless treatment that shows rapid results. Until the ultimate wart treatment is discovered, the patient must be properly educated about HPV viral etiology and specific treatment expectations to avoid frustration for the patient and healthcare provider.

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