

Warts and all

a guide to diagnosis and treatment

Warts affect about 10% of the general population. A very large number will eventually regress spontaneously; nevertheless, patients (or parents) will often be impatient for a quick cure. Care should be taken to ensure the patient has realistic expectations of the range of therapies available.

LINDA PEPALL

MB BS, FACD

Dr Pepall is a dermatologist in private practice, Perth, WA.

Warts are a common and often frustrating clinical problem. They are caused by human papilloma viruses (HPV), a class of double stranded DNA virus, of which there are more than 100 genotypes. Warts are generally classified by their clinical features (common, flat or plane, filiform, mosaic) or by their location (plantar, periungual, facial, mucosal, genital, etc). The box on page 18 outlines the classification of warts.

Epidemiology

Although no accurate figures are available, the incidence of warts in the general population has been estimated at 10%. Warts are most commonly seen in children and young adults. The prevalence of warts in school aged children has

been reported as being between 3 and 20%. Warts are frequently seen in immunosuppressed patients (e.g. transplant patients and people infected with HIV). Studies have shown a 40% prevalence in renal transplant patients (ranging from 15% at the end of the first year to 87% at the end of the fifth year).

Transmission

Transmission of HPV can occur through physical contact or desquamated keratinocytes (e.g. on shower floors). Small breaks in the skin may be required as a point of entry for inoculation to occur. Further warts can develop from autoinoculation. The incubation period from inoculation to clinically apparent warts is not well established,

IN SUMMARY

- The incidence of warts in the general population has been estimated at 10%.
- Transmission of HPV can occur through physical contact or desquamated keratinocytes (e.g. on shower floors).
- Spontaneous regression or resolution occurs in a large number of warts. The average lifespan of cutaneous warts ranges from three months to three years. However, warts may multiply, extend or persist much longer. Rarely, warts can develop into squamous cell carcinomas.
- The differential diagnosis includes seborrhoeic keratoses, ('warty') solar keratoses, keratoacanthomas, squamous cell carcinomas, corns and callosities, lichen planus and, occasionally, molluscum contagiosum.
- The mainstay of treatment still consists of no treatment, topical preparations (e.g. lactic acid and salicylic acid preparations) and/or liquid nitrogen. Probably 99% of warts can be eradicated by using one or a combination of these methods.

but may range from weeks to nine months.

Warts may also 'koebnerise' – that is, spread into an adjacent area of damaged or traumatised skin (Figures 1 and 2). Plane warts can be spread in this way by shaving. Periungual and subungual warts can be spread by cuticle picking and nail biting, respectively. Common warts can be spread by liquid nitrogen treatment – so-called 'satelliting' (when a ring of small warts develops around the central area treated with liquid nitrogen; see Figure 3).



Figure 1. Koebner phenomenon – warts spreading down a superficial scratch mark.



Figure 2. Koebner phenomenon – warts spreading in an area of lichenoid allergic contact dermatitis to the red pigment (cinnabar) in a tattoo.



Figure 3. Koebner phenomenon – 'satelliting' around areas previously treated with liquid nitrogen.

Warts: a guide to diagnosis and treatment

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Most patients consider warts to be a social and cosmetic liability; therefore, the motivation to seek treatment is often quite high, even though many warts eventually regress spontaneously. Care should be taken to ensure the patient has realistic expectations of the range of therapies available.

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Natural history

Spontaneous regression

Spontaneous regression or resolution occurs in a large number of warts; however, once again, there are no accurate figures available. One study observed spontaneous regression for two-thirds of warts in children within two years. It has been suggested that the average lifespan of cutaneous warts ranges from three months to three years. However, warts may multiply, extend or persist much longer. As they are considered by most patients to be a cosmetic and social liability, the motivation to seek treatment is generally quite high.

Classification of cutaneous warts

Classification by clinical features



Figure A. Common warts (*verruca vulgaris*).



Figure B. Plane warts on the chin.

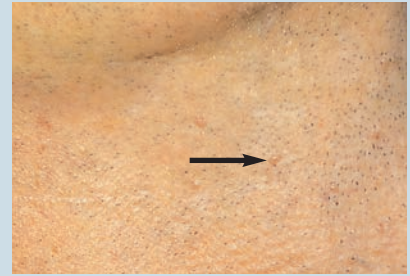


Figure C. Plane (or flat) warts on the neck.

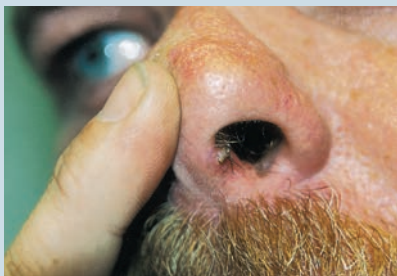


Figure D. Filiform wart (crusted).



Figure E. Mosaic wart (partially treated with 3% formalin).

Classification by location



Figure F. Plantar wart.



Figure G. Periungual wart.



Figure H. Periungual and subungual wart.



Figure I. Mucosal warts.



Figure J. Penile warts.

Malignant transformation

Rarely, warts can develop into squamous cell carcinomas. Certain subtypes of HPV are more likely to have malignant potential. Malignant transformation is most often seen in genital warts (e.g. HPV-16 and -18). However, HPV has been associated with longstanding warts on fingers developing into squamous cell carcinoma. Immunosuppressed patients (especially after transplantation) are more likely to experience malignant transformation. Rarely, HPV can induce the development of a Buschke Lowenstein tumour, an extremely large slow-growing anogenital squamous cell carcinoma.

A rare condition, epidermodysplasia verruciformis, is an inherited disorder in which there is widespread and persistent infection with the wart virus. The warts in this condition are usually flat, like plane warts, and often coalesce into reddish plaques. Malignant change is common but metastases are rare. Impairment of cell-mediated immunity is commonly found in these patients, although they are not usually susceptible to other infections.

Differential diagnosis

In the vast majority of cases, warts are a spot diagnosis. However, several conditions can on occasion cause confusion (Table 1). Seborrheic keratoses (Figure 4) can mimic viral warts, as can ('warty') solar keratoses, keratoacanthomas and squamous cell carcinomas.

Corns and callosities can be easily confused with plantar warts, and lichen planus (Figures 5 and 6) can be mistaken for plane warts or flat genital warts. Occasionally, molluscum contagiosum (Figure 7) can also cause a diagnostic dilemma.

Carefully paring down a keratotic lesion with a scalpel blade to look for the characteristic 'dots' (thrombosed capillaries) seen in warts can help confirm the diagnosis. Note that vigorous

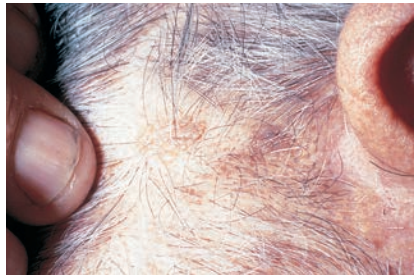


Figure 4. Seborrheic keratosis. This condition can mimic viral warts.



Figure 6. Lichen planus of the penis. This condition can be mistaken for flat genital warts.

paring results in bleeding and can cloud the diagnosis further.

Choosing treatment

There is a myriad of treatment options available. The choice of therapy depends on:

- the location, numbers, size and type of the wart
- the patient
- the practitioner's experience and skill with various treatment modalities (Table 2).

Table 1. Differential diagnosis

- Seborrheic keratosis
- Solar keratosis
- Keratoacanthoma
- Squamous cell carcinoma
- Callosity, corn or clavus
- Lichen planus
- Molluscum contagiosum



Figure 5. Lichen planus of the skin. This condition can be mistaken for plane warts.



Figure 7. Molluscum contagiosum can cause a diagnostic dilemma.

Table 2. Factors influencing choice of treatment

Wart

- Size
- Number
- Duration
- Location
- Type

Patient

- Age
- Immune status
- General health
- Stoicism
- Personal preference
- Ease of attendance
- Socioeconomic status

Physician

- Skill
- Experience
- Preference

In the absence of specific antiviral therapy, wart treatments are aimed at removing the protective keratin layer overlying the wart and/or stimulating an immune response.

Mainstays of treatment

The mainstays of treatment still consist of three options:

- no treatment
- topical preparations (e.g. lactic acid and salicylic acid preparations)
- liquid nitrogen.

Probably 99% of warts can be eradicated by using one or a combination of these methods. Truly resistant warts can be treated by a variety of other methods.

No treatment

It is an option not to treat warts. Masterly inactivity has a reasonably high success

rate. It is particularly reasonable if the wart has not been the patient's primary reason for presentation but has been mentioned as an afterthought. It is reasonable to suggest that the wart may well disappear of its own accord, and to offer the patient a follow up appointment if the wart has not gone in three months, or if it has multiplied or enlarged during that period.

Topical preparations

Try simple, safe, painless treatment first. Topical preparations (e.g. lactic acid and salicylic acid preparations) do work – 70 to 80% of warts can be cleared in 8 to 12 weeks. It is imperative to emphasise the importance of compliance; patience and persistence are required.

Many patients feel that three to five applications are sufficient effort to remove the wart. It is essential to explain that the treatment needs to be applied every day for 12 weeks, filing the wart back with an emery board each night prior to each fresh application. The wart can then be covered, if desired, with adhesive tape to enhance the penetration and destructive effect of the paint. If the wart disappears in less than 12 weeks, patients feel they have had a real win.

Most treatment failures occur because patients get sick of applying the treatment and therapy lapses. Tell patients to return for other therapy only if they have applied the topical preparation every day for 12 weeks or used up an entire bottle of treatment, whichever occurs first.

Significant inflammation or infections are rare with the above preparations if they are used correctly. If the area becomes too tender during the treatment period, a break from treatment may be taken (maximum, three to five days). Small warts may be treated using a toothpick as an applicator.

Liquid nitrogen

Liquid nitrogen is generally a very effective therapy for warts; however, it is painful. For this reason, it is not ideal

for children younger than 12 years, unless they (as opposed to their parents) are strongly motivated for a quick cure.

I generally offer the patient a choice between the slow, tedious, painless method (topical preparations) and the quick, painful method (liquid nitrogen). My usual approach would be to suggest a 12-week trial of a topical preparation with the 'threat' of liquid nitrogen if the patient has not managed to eradicate the warts by then.

The technique of liquid nitrogen therapy is quick and simple. Liquid nitrogen may be applied with an open spray technique or by direct application using a cotton tip. The application of liquid nitrogen is continued until a rim of freezing (lateral spread of freezing, extent of ice ball) is 1 to 2 mm beyond the wart. This generally takes 10 to 15 seconds.

The likelihood of success of the therapy is enhanced if this sized ice ball can be maintained (not further enlarged) for another 10 to 15 seconds. The patient needs to be aware that one application does not necessarily cure a wart. Generally three applications are required, ideally at three-weekly intervals.

Many aspects need to be considered before embarking upon liquid nitrogen therapy. The patient must be advised of what to expect from the treatment (Table 3). Certain patients may not be suitable for liquid nitrogen therapy because of their age, occupation or hobbies (liquid nitrogen therapy to the hands of a concert pianist or the feet of a ballroom dancer may not be the most appropriate choice of therapy). Darkly pigmented patients are generally not suitable for liquid nitrogen therapy because of the high incidence of hypopigmentation with therapy.

Occasionally medical diseases, such as cold urticaria, cryofibrinogenaemia, cryoglobulinaemia, peripheral vascular disease, severe diabetes or Raynaud's disease, may necessitate the use of alternative forms of therapy.

It is important to distinguish between

Table 3. Liquid nitrogen therapy for warts

Expected sequelae

- Pain
- Inflammation
- Oedema
- Blistering (may be haemorrhagic)

Complications

- Recurrence
- Satellites (ring of small warts developing around central treated area)
- Bleeding (if debulked first)
- Hypopigmentation (usually permanent)
- Scarring
- Syncope
- Delayed healing (lower legs)
- Infection*
- Nerve damage*
- Tendon rupture*
- Milia*
- Pyogenic granuloma*
- Ectropion or deformity*

* These complications are rare.

continued



Figure 8a. Reaction to liquid nitrogen therapy – extreme haemorrhagic blistering.



Figure 8b. Resolution of blisters.

FIGURE 8 COURTESY OF DR P. RANDELL

Table 4. Treatment options for warts

Topical preparations

- Lactic acid or salicylic acid
- Podophyllin or podophyllotoxin*
- Formalin or glutaraldehyde
- Tretinoin*
- Trichloroacetic acid
- Cantharadin†
- Dinitrochlorobenzene or diphencyprone††
- Silver nitrate
- Imiquimod (genital warts)*

Destructive or surgical modalities

- Liquid nitrogen
- Cautery or diathermy
- Excision
- Laser
- Superficial x-ray therapy*‡

Intralesional therapy

- Bleomycin*
- Interferon*

Oral or systemic therapy

- Retinoids*
- Cimetidine†§

Alternative or adjunctive therapy

- Hypnosis
- Acupuncture
- Placebo

* Not suitable during pregnancy. † Not approved by Therapeutic Goods Administration for this use. ‡ Rarely used these days. § Experimental.

the expected sequelae and the complications of liquid nitrogen therapy (Table 3). Reactions that ensue after freezing include erythema then vesiculation, oedema, exudation and sloughing.

Pain is the main disadvantage of the treatment. Usually it is short-lived, initially lasting from a few to 10 minutes. This is followed by swelling, which may be dramatic in the areas of lax skin (e.g. the periorbital area).

Blistering (sometimes haemorrhagic) is common and can be marked, especially on the dorsum of the hands in elderly patients (Figure 8), although it is not necessarily a prerequisite for resolution of the wart. Ideally, blistering should be limited to 1 to 2 mm greater than the diameter of the wart.

Healing usually takes two to three weeks. Scarring is unlikely for freezing times less than 30 seconds. Depigmentation is common in darkly pigmented skin and is usually permanent.

Other forms of treatment

A myriad of other therapies has been described for treating warts (Table 4). However, it is important not to be pressured into inappropriate, invasive, toxic, destructive or experimental therapies by impatient patients.

Topical preparations for resistant warts

- Podophyllin and podophyllotoxin (Condyline Paint) are useful therapies but are generally most effective in

genital warts (because they are less keratinising than cutaneous warts). Podophyllin is made up in strengths of 15 to 50% in tincture of benzoin compound (friar’s balsam) by the chemist for the doctor’s use. It is also available over the counter in Posalfin, but in this particular formulation is contraindicated for use in anogenital warts (because of the presence of other active ingredients).

- **Extemporaneous recipes** can be resorted to, if required (e.g. 20% formalin, 20% acetate and 20% salicylic acid in flexible collodion).
- **Formalin soaks** (3 to 6 %) can be effective; however, they can cause significant drying and irritation to the surrounding skin. Protect surrounding skin with a layer of petroleum jelly prior to soaking the wart. Contact sensitisation is also a possibility (although not common). This is also true of glutaraldehyde.
- **Trichloroacetic acid, silver nitrate and other highly irritant chemicals** can be used but may cause significant pain.
- **5-Fluorouracil** (5%) can be used in combination with salicylic acid. However, hyperpigmentation, erythema and erosion can occur, as can onycholysis (lifting of the nail plate from the nail bed) if this treatment is used periungually.
- **Cantharadin**, a powerful vesicant, can be very useful in the treatment of warts. However, it can cause spectacular blistering and is not registered by the TGA for medical use in Australia.
- **Allergic contact sensitisation (immunotherapy)** with dinitrochlorobenzene or diphencyprone can also be effective. The technique involves first sensitising the patient to the compound, then applying gradually increasing strengths in order to elicit an allergic contact dermatitis (stimulated immune response). Complications range from mild itching to florid blistering contact dermatitis.

Surgical treatment

Surgical or destructive therapies can certainly be effective. However, if warts recur in scar tissue they are even more recalcitrant. Surgery and cautery are generally not recommended for plantar warts, because scar tissue on the sole of the foot can be more of an inconvenience to the patient than the original wart itself.

Carbon dioxide laser can be particularly effective for periungual warts; however, it is not a panacea and the usual complications of scarring and recurrence are still a problem.

Superficial x-ray therapy is rarely used these days because of the deterioration of postradiation scarring years after treatment.

Intralesional therapy

Intralesional bleomycin

Intralesional bleomycin can be used to treat refractory warts. Usually one to two injections (between 0.2 and 1 mL of 1 U/mL solution) are required.

Local anaesthetic cover is generally required because bleomycin injections are painful. Raynaud's phenomenon can occur in treated fingers, as can nail loss or dystrophy.

Bleomycin is an excellent treatment for extremely recalcitrant plantar warts. However, the expense of a single ampoule of bleomycin generally limits its use to public teaching hospitals.

Intralesional interferon

Intralesional interferon (Intron A) has been reported to be of varying use in cutaneous warts. Spectacular anecdotal results have been achieved in the treatment of common warts (Figure 9). However, the results of placebo-controlled, double-blind studies are generally disappointing. Genital warts are currently the only approved indication (see below).

Systemic therapy

Systemic therapy for warts is rarely justified. Oral retinoids can be useful in

exceptional situations (e.g. transplant patients and epidermodysplasia verruciformis patients).

An uncontrolled report quoted impressive results with the use of cimetidine in children with warts (20 to 40mg/kg for four months). However, equally impressive double-blind, placebo-controlled trials have not been forthcoming. In fact, a recent such trial showed no advantage over placebo.

Although cimetidine is a reasonably innocuous drug, it must be remembered that it is not currently approved for use in children and thus this form of therapy is still essentially experimental.

Treatment of specific types of warts

Plane warts

Plane warts are small flat-topped papules. They have a very fine warty surface that is generally only apparent on close inspection (Figures B and C in the box on page 18). They commonly occur on the face, the dorsum of the hands and wrists, and the lower legs.

When present in not too great a number, plane warts can easily be treated with a light spray or dab (a few seconds) of liquid nitrogen.

When present in larger numbers, mild topical keratolytics such as 2.5 to 5% benzoyl peroxide (Benzac, Brevoxyl, Clearasil Ultra, Oxy, Panoxyl) or 0.025 to 0.05% topical tretinoin (Retin-A, Retrieve Cream, Stieva-A) are usually effective. These preparations can be quite irritating and some patients may initially need to use the lowest strength every second or third night until greater skin tolerance is developed. It may take 12 weeks for treatment to be effective.

Plantar warts

Plantar warts (Figure F in the box on page 18) can be troublesome, persistent and painful. Paring down the keratotic element of plantar warts not only reduces the pain upon walking, it also



Figure 9a. Multiple hand warts ('butchers' warts').



Figure 9b. Resolution after intralesional interferon.



Figure 10. Liquid nitrogen reaction: blistering of the sole of the foot.

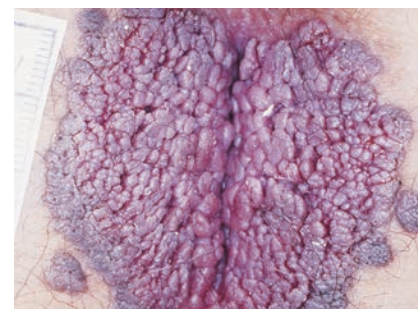


Figure 11. Condylomata acuminata.

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improves the effectiveness of therapy.

Treatment with topical keratolytics, as outlined above, can be very effective in treating plantar warts. Preparations containing strengths of salicylic acid greater than the 17% found in most over the counter preparations available for the treatment of common warts may be required.

For persistent plantar warts, liquid nitrogen is also effective; however, painful blisters can be a problem (Figure 10). Upton's paste (6 parts salicylic acid to 1 part trichloroacetic acid) or 70% salicylic acid paste can also be used. Apply elastoplast to the surrounding skin for protection, then apply the paste under a second layer of elastoplast and leave it intact for one week. Several weeks' therapy is usually required. The area becomes macerated and smelly; therefore, this is often not an acceptable form of therapy for patients who are physically active or who have sweaty feet. It is useful in older patients who have difficulty reaching their soles and applying daily treatments.

Genital warts

Causes

Genital warts (Figure 11) are most commonly caused by HPV-6 and -11. However, oncogenic genotypes HPV-16 and -18 may also be present.

All women with genital warts and female sexual partners of men with genital warts need to have regular Pap smear examinations to check for the presence of cervical HPV cell changes.

The incubation period from contact to development of warts is poorly documented but is thought to range from three weeks to nine months or more (possibly years). The average incubation period has been suggested to be three months. Although not well documented, it has been suggested that subclinical or latent HPV may persist for years.

Genital warts may be the cauliflower-like condyloma acuminata, or papular, filiform or flat.

Treatment

Treatment of genital warts can be very frustrating, because of the high rate of recurrence after apparent clinical cures. Visualisation of clinically inapparent warts can be enhanced by applying 5% acetic acid (straight white vinegar will do) for three minutes. The warts turn white, enhancing their contrast to the surrounding normal skin (so-called 'aceto-whitening').

Treatment options are outlined in the sections below.

Chemical cytotoxics

- Podophyllin (10 to 25% in friar's balsam) – applied weekly by a physician and washed off by the patient, initially after four hours, with duration gradually increased to 8 to 10 hours.
- Podophyllotoxin (0.5%) – applied by the patient twice daily for three days, followed by a four-day break from therapy. Repeated for up to six weeks.
- Trichloroacetic acid (65 to 80%) – applied weekly by a physician and left on by the patient. Can cause considerable pain if it spreads onto surrounding skin. Protect surrounding skin with petroleum jelly prior to application.

Physical or ablative therapy

- Liquid nitrogen – a 10- to 20-second 'freeze', applied weekly by a physician until clinical resolution. Generally, if the warts have not cleared by six treatments (maximum 10), some other form of therapy should be tried.
- Laser – generally a CO₂ laser is used. This is a good option for ablating very bulky warts. Virus particles have been reported in laser plumes.
- Electrosurgery (diathermy and cautery) – studies have shown viable HPV in laser and diathermy plumes.

Immunomodulation

- Imiquimod (5% cream [Aldara]) – applied three times a week for 4 to 16 weeks. Stimulates production of interferon and cytokines. Applied by the patient every second day and washed off after 10 hours. Good clearance rates and generally good acceptability by patients. Side effects include irritation, redness and oedema. This treatment is currently still expensive (although covered by many private health funds) and is not suitable for use during pregnancy.
- Intralesional interferon (alpha 2b) – injected three times a week for three weeks. Limited by expense of treatment and 'flu-like' side effects. Intralesional interferon treatment is not suitable for use during pregnancy.
- Cidofovir – a promising new antiviral agent currently under investigation for the treatment of genital warts.
- Vaccines – potentially a hope for the future?

Summary

From the outline of therapies above, it can be seen that there is still no 'magic bullet' for the treatment of warts. The mainstays of treatment are still:

- no treatment
- topical preparations (e.g. lactic acid and salicylic acid preparations)
- liquid nitrogen.

Probably 99% of warts can be eradicated by using one or a combination of these methods. Truly resistant warts can be treated by a variety of other methods (see Table 4).

With all these treatments available, special attention should be paid to ensuring that the patient understands the chosen procedure and its limitations and complications, and has realistic expectations.

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