

Guidelines for the management of cutaneous warts

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Summary

These guidelines for the management of cutaneous warts have been prepared for dermatologists on behalf of the British Association of Dermatologists. They present evidence-based guidance for treatment, with identification of the strength of evidence available at the time of preparation of the guidelines, and a brief overview of epidemiological aspects, diagnosis and investigation.

Disclaimer

These guidelines have been prepared for dermatologists on behalf of the British Association of Dermatologists and reflect the best data available at the time the report was prepared. Caution should be exercised in interpreting the data; the results of future studies may require alteration of the conclusions or recommendations in this report. It may be necessary or even desirable to depart from the guidelines in the interests of specific patients and special circumstances. Just as adherence to guidelines may not constitute defence against a claim of negligence, so deviation from them should not necessarily be deemed negligent.

Definition

Warts are caused by infection of the epidermis with human papillomavirus (HPV). HPVs are divided into separate genotypes on the basis of their DNA sequence. Different HPV types may preferentially infect either cornified stratified squamous epithelium of skin or uncornified mucous membranes. The appearance of the lesion is influenced not only by viral type but also by environmental and host factors.

These guidelines omit detail regarding therapy for anogenital warts. Patients with such warts are best seen and investigated by genito-urinary physicians to exclude the possibility of other sexually transmitted

disease. Children with ano-genital warts, particularly over the age of 3 years, may need paediatric assessment if sexual abuse is considered a possibility.

Epidemiology and prevalence

Most people will experience infection with HPV at some time in their life. The prevalence of viral warts in children and adolescents in the United Kingdom has been recorded at between 3.9% and 4.9%.¹ Other surveys in the northern hemisphere quote prevalence rates of between 3% and 20% in children and teenagers^{2–4} and 3.5% in adults aged 25–34 years.^{5,6}

There are marked regional differences in wart prevalence, rates being higher in the north than in the south of the U.K. Visible warts were twice as common in white Europeans compared to other ethnic groups in the National Child Development Study of 1958.⁷ This study also suggests that in 90% of children, warts at the age of 11 years had cleared by the age of 16 years. Other studies have suggested spontaneous clearance rates of 23% at two months, 30% at 3 months and 65–78% at 2 years.^{2,3,8–10}

Most large studies have found no evidence of a sex difference in wart prevalence.¹ Population studies suggest that there is no increased risk of viral warts in children with atopic eczema.¹¹

Common forms of warts and their HPV type are described in Table 1.

Other warty conditions

Epidermodysplasia verruciformis

Epidermodysplasia verruciformis (EV) is an inherited disorder in which there is a mild defect of cell-mediated

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Table 1. Morphology of warts

Clinical type	Appearance	HPV type
Common warts	Firm, rough keratotic papules and nodules on any skin surface. May be single or grouped papules.	1,2,4,57
Plane warts (flat warts)	2–4 mm in diameter, slightly elevated. Most commonly flat topped papules with minimal scaling.	3,10
Intermediate warts	Features of common and plane warts.	2,3,10,28
Myrmecia	Deep burrowing wart.	1
Plantar warts	May start as sago grain-like papules which develop a more typical keratotic surface with a collar of thickened keratin.	1,2,4,57
Mosaic warts	Occur when palmar or plantar warts coalesce into large plaques.	2
(Ano) Genital warts	Epidermal and dermal nodules and papules in the perineum and on the genitalia.	6,11
(Condyloma acuminata or venereal warts)	Their occurrence in children especially under the age of 3 is not always a sign of sexual abuse; vertical transmission is possible.	
Oral warts	Small white or pink elevated papules on the oral mucosa. (HPV 16 has been detected in 80% of cases of oral leukoplakia.)	6,11,32

immunity and widespread and persistent infection with HPV. The lesions vary considerably and may be flat, wart-like lesions, often pigmented, red or atrophic macules or branny pityriasis versicolor-like plaques. The flat, wart-like lesions are frequently localized to the extremities and the face and thicker plaques may resemble seborrheic keratoses. The lesions are found to harbour a large variety of HPV types including those causing plane warts, but also several which do not cause disease in normal individuals. There is a risk of development of squamous cell carcinoma on sun-exposed skin.

Bowenoid papulosis

Also known as vulval, penile and anal intraepithelial neoplasia (VIN, PIN, AIN), Bowenoid papulosis presents as small papules, usually multiple, sometimes pigmented, on the cutaneous and mucosal surfaces of the ano-genital regions in both sexes. It usually affects young adults but no age is exempt and there is a strong association with HPV 16 infection.

Focal epithelial hyperplasia

Also known as Heck's disease, this is a rare benign, familial disorder with no sex predisposition. It is characterized by multiple soft circumscribed sessile nodular elevations of the oral mucosa. The disease is seen most commonly in native Americans and in Inuits in Greenland but has been reported rarely from many other countries. HPV 13 and HPV 32 appear to be the causal agents in patients with a genetic predisposition.

Epithelioma cuniculatum and verrucous carcinoma

Epithelioma cuniculatum is a squamous cell carcinoma that appears as a soft bulbous mass with a squashy consistency on the sole of the foot. Multiple sinuses open onto the surface and when pressed, the lesion may appear like a giant plantar wart, but is distinguished by its relentless growth and local invasion. Verrucous carcinoma may develop in the oral cavity and on the genital mucosa and appear as cauliflower-like lesions. The bland histology contrasts with its aggressive behaviour.

Diagnosis

Diagnosis of warts is usually based on clinical examination but can be suggested by the histological appearances of acanthotic epidermis with papillomatosis, hyperkeratosis and parakeratosis, with elongated rete ridges often curving towards the centre of the wart. Dermal capillary vessels may be prominent and thrombosed. There may be large keratinocytes with eccentric pyknotic nuclei surrounded by a perinuclear halo (koilocytes are characteristic of HPV-associated papillomas). HPV infected cells may have small eosinophilic granules and diffuse clumps of basophilic keratohyaline granules. These are not HPV particles. Flat warts have less acanthosis and hyperkeratosis and do not have parakeratosis or papillomatosis.

HPV typing is limited to a few laboratories but may be useful in some cases of genital warts in children with suspected sexual abuse. Knowledge of the HPV genotype in benign warts does not influence choice of therapy.

Table 2. Summary of treatments for warts

Strength of evidence	Treatment	Suggested method of use
A, I	Cryotherapy	15–20 s single or double freeze of warts, every 3–4 weeks
B, I	Photodynamic therapy	3 treatments: 20% topical amino-laesulinic acid + irradiation
B, II ii	Salicylic acid (SA)	Daily application of 15–20% SA in suitable base. 25–50% SA may be used cautiously on plantar warts. 2–5% SA cream may be used for plane face warts.
	Bleomycin	Single intralesional delivery
	Retinoids	Topical: 0.05% tretinoin cream daily Systemic: 1 mg/kg/day acitretin for 3 months
C, II ii	Formaldehyde	Daily application of 0.7% gel or 3% solution as short soak for mosaic plantar warts
C, III	Thermocautery	Single surgical removal of wart; risk of scarring
	Glutaraldehyde	Daily application of 10–20% in suitable base.
C, IV	Chemical cautery	Twice weekly application
	CO ₂ laser	Single treatment
	Pulsed dye laser	Single treatment
	Topical sensitization	Sensitization with 2% diphenylprone, then weekly application of appropriate dilution of the allergen.
D, I	Cimetidine, oral	Up to 40 mg/kg/day for 3 months
	Homeopathy	
Insufficient evidence	Podophyllin	
	Folk remedies	
	Hypnosis	
	Heat treatment	
	Interferon	
	Imiquimod	

Differential diagnosis

Plantar warts must be distinguished from callosities which are ill-defined areas of waxy, yellowish thickening, which on paring reveal no capillaries. Corns occur on pressure points and are usually smaller and painful with a central plug. Plane warts must be distinguished from lichen planus which will normally show a violaceous discoloration and Wickham's striae. The lesions of lichen planus are usually pruritic and often accompanied by characteristic mucosal lesions. Epidermal naevi may resemble clusters of filiform and digitate warts. The individual lesions of molluscum contagiosum are white umbilicated papules sometimes showing a central depression.

Transmission of warts

Warts are spread by contact, either directly from person to person, or indirectly via fomites left on surfaces. Infection via the environment is more likely to occur if the skin is macerated and in contact with roughened surfaces, the conditions which are common in swimming pools and communal washing areas.¹²

Warts and malignancy

Benign warts in immunocompetent individuals almost never undergo malignant transformation. There are a small number of reports of lesions that have initially appeared as warts and later become invasive squamous cell carcinomas. Periungual warts in combination with genital HPV disease warrant particular attention.

Warty lesions are especially common in immunosuppressed and transplant patients – approximately 50% of renal transplant patients develop warts within 5 years of transplantation.¹³ Sun exposure increases the incidence of warty lesions and also acts as a cocarcinogen. Dysplastic change is quite common and there is frequently poor correlation between clinical and histological appearances. The lesions may appear typical of virus warts, solar or Bowenoid keratoses or keratoacanthomata or occasionally frank squamous carcinomata. Numerous HPV types have been found in benign and malignant squamous lesions in immunocompromised patients and the precise role they play in initiation and progression of malignancy is yet to be elucidated.

Table 3. Treatments for consideration according to site of warts

Face	Hands	Feet	Body
Consider no treatment	Consider no treatment	Consider no treatment	Consider no treatment
Plane warts	(1)	(1)	Single
Salicylic acid (cream)	Salicylic acid paint	Salicylic acid paint	Curettage + cautery
Cryotherapy	Glutaraldehyde	Glutaraldehyde	Cryotherapy
Curettage + light cautery	Formaldehyde	Formaldehyde	
Filiform warts	(2)	(2)	Multiple
Cryotherapy	Cryotherapy	Cryotherapy	Cryotherapy
Curettage + light cautery	Curettage + cautery	Silver nitrate	Curettage + cautery
	Silver nitrate		Retinoid, systemic
	(3)	(3)	
	PDT	PDT	
	Bleomycin	Bleomycin	
	CO ₂ laser	CO ₂ laser	
	Pulsed dye laser	Pulsed dye laser	
	Retinoid, systemic	Retinoid, systemic	
	Topical immunotherapy	Topical immunotherapy	

Published evidence is inadequate to permit development of clear rules for treating particular types of warts in specific sites in individuals of various ages. The above-mentioned therapies could all be considered alone, sequentially or in combination. Treatment in groups (1) or (2) could be performed by general practitioner but those in group (3) are more specialized.

Treatment

There is no single treatment that is 100% effective and different types of treatment may be combined. Research into efficacy of treatment must take into account the possibility of spontaneous regression. It is a valid management option to leave warts untreated if this is acceptable to patients but plantar warts can be painful and hand warts sufficiently unsightly to affect school attendance or cause occupational difficulty. Warts in adults, in those with a long duration of infection and in immunosuppressed patients are less likely to resolve spontaneously and are more recalcitrant to treatment.^{14–16}

Different types of warts and those at different sites may need differing treatments.¹⁷ Genital warts are not dealt with in depth in these guidelines. Facial warts should not be treated with wart paints because of the risk of severe irritation and possible scarring. Plane warts Koebnerize readily and any destructive technique may exacerbate the problem. The majority of warts can be treated in general practice and increasingly, wart clinics are run by nursing staff. A summary of treatments is given in Tables 2 and 3.

The ideal aims of treatment of warts are: (i) to remove the wart with no recurrence; (ii) to produce no scars; and (iii) to induce life-long immunity. Certain general principles in the treatment of warts should be observed:

- 1 Not all warts need to be treated
- 2 Indications for treatment are: pain; interference

with function; cosmetic embarrassment; and risk of malignancy

3 No treatment has a very high success rate (average 60–70% clearance in 3 months)

4 An immune response is usually essential for clearance. Immunocompromised individuals may never show wart clearance.

5 Highest clearance rates for various treatments are usually in younger individuals who have a short duration of infection.

Destructive treatments

Salicylic acid (Strength of evidence [Appendix]: B, Iii). Salicylic acid is a keratolytic that acts by slowly destroying the virus-infected epidermis. The resulting mild irritation may stimulate an immune response. Salicylic acid alone has been shown to produce clearance in 67% of patients with hand warts and 84% in those with plantar warts in 12 weeks.¹⁴

There are many commercially available preparations but there is limited information to enable comparison to be made between products:

1 Salicylic acid 11–17% in collodion and collodion-like gels ± lactic acid, copper.

2 Salicylic acid 26% in polyacrylic base – designed to be self-occlusive.

3 Salicylic acid 25% with podophyllin in ointment base – for use on plantar warts.

4 Salicylic acid 50% ointment for use on plantar warts.

Before application of wart paints, excess keratin should be pared away or filed with sandpaper or emery board and the area softened by soaking in warm water. Collodion-based products form a film that should be peeled off before re-application. Occlusion has been shown to improve clearance rates of plantar warts.¹⁸

Comparisons between salicylic acid-containing paints, and monotherapy with glutaraldehyde, fluorouracil, podophyllin, benzalkonium or liquid nitrogen cryotherapy, failed to find any preparation more effective than salicylic acid.¹⁴

Cryotherapy (Strength of evidence: A, I). Liquid nitrogen (LN₂, -196 °C) is the most commonly used agent. Carbon dioxide slush (-79 °C) is now less commonly used. Dimethyl ether/propane mixtures (-57 °C) are used because of their convenience but efficacy in inducing tissue temperatures adequate for cell necrosis appears low.¹⁹ Cryotherapy may have an effect on wart clearance either by simple necrotic destruction of HPV-infected keratinocytes, or possibly by inducing local inflammation conducive to the development of an effective cell-mediated response.

Techniques differ between practitioners with variations in freeze times, mode of application and intervals between treatment. Many practitioners use a spray, but cotton wool-tipped sticks are still widely used and can be preferable when treating children or for warts near the eyes. It is common practice to freeze until a halo of frozen tissue appears around the wart and then time for 5–30 s depending on site and size of wart. When reapplying LN₂ with a cotton stick it is important to be aware that HPV and other viruses such as HIV can survive in stored liquid nitrogen.

Destruction of warts by freezing every three weeks can give a clearance rate of 69% of patients with hand warts in 12 weeks.¹⁴ This study used liquid nitrogen applied with a cotton bud until a frozen halo appeared round the wart (5–30 s). Clearance rates are increased when cryotherapy is combined with salicylic acid paints although this did not reach significance.¹⁴

Two freeze–thaw cycles have been shown to improve clearance in plantar warts but not in hand warts.²⁰ The ideal interval between freeze treatments is unclear – Bunney's study showed that intervals above 3 weeks reduced cure rates at 12 weeks,¹⁴ others have shown that clearance was dependent on the number of treatments so that weekly treatments resulted in more rapid clearance.²¹

Patients should be warned that cryotherapy is painful and blistering may occur. Caution must be used when freezing warts over tendons and in patients with poor circulation. Hypo- and hyper-pigmentation can occur, particularly in black skin. Onychodystrophy can follow treatment of periungual warts.

Thermocautery/curettage and cautery (Strength of evidence: C, III). Surgical removal of warts is widely practised, particularly by curettage or blunt dissection, followed by cautery. It may be particularly useful for filiform warts on the face and limbs. In open studies, a patient success rate of 65–85% is reported.^{22,23} Scarring is usual after these procedures and recurrence occurs in up to 30%. The development of scarring is a relative contraindication to this form of surgery on the sole.

Chemical cautery: silver nitrate stick (Strength of evidence: C, IV). Chemical cautery with repeated daily use of silver nitrate stick can induce adequate destruction to effect wart clearance, but occasionally pigmented scars may develop. In a placebo-controlled study of 70 patients, three applications of silver nitrate over nine days resulted in clearance of all warts in 43% and improvement in warts in 26% one month after treatment compared to 11% and 14%, respectively, in the placebo group.²⁴

Carbon dioxide laser (Strength of evidence: C, IV). The destruction produced by the CO₂ laser has been used to treat viral warts. Periungual and subungual lesions, which can be difficult to eradicate by other methods, may be particularly appropriate for this treatment. A cure rate of individual warts of 64–71% at 12 months is reported in two case series^{25,26} but postoperative pain and scarring may occur.

Pulsed dye laser (Strength of evidence: C, IV). The use of the pulsed dye laser depends upon the energy absorption within the capillary loops of the wart and hence localized tissue necrosis. Uncontrolled studies have suggested a wart clearance rate of 70–90%^{27,28} and a patient clearance rate of 48%.²⁹ Pain and scarring are less than with the CO₂ laser.

Photodynamic therapy (Strength of evidence: B, I). This treatment depends upon the uptake by abnormal cells of a chemical, usually amino-laevulinic acid (ALA), involved in the porphyrin pathway and subsequent photo-oxidation invoked by irradiation using laser or non-laser light of affected tissue. Comparison of

response in 45 patients who received 3 treatments of 589–700 nm laser light after application of either 20% ALA or placebo cream showed that the active treatment produced a significant improvement in clearance or reduction of wart size after 4 months with ALA and irradiation.³⁰

Virucidal Methods

Formaldehyde (Strength of evidence: C, Iii). Formaldehyde is virucidal and is available commercially as a 0.7% gel or a 3% solution. As a soak it may hasten clearance of viral warts when combined with regular paring. Two hundred children with plantar warts were treated for 6–8 weeks with 3% formaldehyde solution and this produced clearance in 80% of warts.²² A controlled study comparing formaldehyde soaks with both water soaks and with saccharose by mouth showed no difference in wart clearance rates between the three groups.³¹

Glutaraldehyde (Strength of evidence: C, III). Glutaraldehyde is available as a 10% solution or gel and like formaldehyde it hardens the skin and makes paring easier. An uncontrolled trial with a 20% solution applied once daily cleared warts in 72% of 25 patients in three months.³² It has the disadvantage of staining the skin brown and there has been a report of cutaneous necrosis following the application of 20% glutaraldehyde.³³

Antimitotic therapy

Podophyllin/Podophyllotoxin. Podophyllotoxin, the active ingredient within the cruder mixture of podophyllin, acts as an antimitotic by binding to the spindle during mitosis. Cellular division is blocked. The agent is used extensively in the treatment of anogenital warts, but penetration of a thick stratum corneum is poor and podophyllin is much less effective in the treatment of skin warts. Applied under occlusion after paring of the wart (see Keratolytics section), the treatment may be effective³⁴ but there is risk of intense inflammation, sterile pustule formation and secondary infection.

Bleomycin (Strength of evidence: B, Iii). Intralesional application of the cytotoxic agent bleomycin³⁵ has been used to treat warts that have failed to respond to other modalities of treatment. Studies have used concentrations of bleomycin of 250–1000 U/mL (old units 0.25–1 U/mL) with no obvious benefits for the higher

concentrations.³⁶ Response rates of between 31% and 100% are reported.

Pain both on application and afterwards is the main limiting factor. The resultant necrosis can cause scarring, pigmentary change and nail damage. Injected or topical local anaesthesia is often needed. Bleomycin may be injected with a normal syringe but studies have also looked at using modified tattooing apparatus, dermal multipuncture injection or simply applying a drop of bleomycin and pricking the wart repeatedly with a Monolet™ needle. The latter uncontrolled study of 62 patients treated monthly gave a success rate of 92% of treated individuals after an average of four months.³⁷ Bleomycin should not be used in pregnant women since significant absorption of bleomycin has been reported following intralesional injection.³⁶

Retinoids (Strength of evidence B, Iii). Retinoids disrupt epidermal growth and differentiation thereby reducing the bulk of the wart. A randomized controlled trial of 25 children treated with 0.05% tretinoin cream showed clearance rates of 85% of the children compared with 32% in 25 controls.³⁸ There are a number of case reports and a limited number of trials showing the effect of systemic retinoids in the treatment of warts.^{39,40} Sixteen of 20 children with extensive warts given etretinate for a period not exceeding 3 months at a dosage of 1 mg/kg per day showed complete regression of the disease without relapse.⁴¹ In 4 patients the lesions recurred following partial regression.

Immune stimulation

Topical sensitization (Strength of evidence: C, IV). The induction of delayed hypersensitivity has been used as a treatment of warts. Dinitrochlorobenzene⁴² and squaric acid dibutylester⁴³ have been used but most studies have looked at the effect of diphencyprone. Two large open studies of diphencyprone have shown encouraging results. In one, diphencyprone was applied weekly for 8 weeks in 134 patients and gave a response rate of 60% (complete clearance 44% of individuals at 4 months).⁴⁴ In another retrospective study, of 48 patients treated on average every 3 weeks, 88% of patients were clear of warts within 14 weeks.⁴⁵ Drawbacks of this treatment are that some patients cannot be sensitized whilst others get troublesome eczematous reactions.

Cimetidine (Strength of evidence: D, I). Cimetidine has weak, undefined immunomodulatory effects and its use

to treat warts has been advocated. Several open trials suggested efficacy, but a controlled trial showed no advantage over placebo.⁹

Other treatments

Many other treatments have been used to treat warts, although few have received adequate assessment.

Folk remedies^{45,46} are still practised but remain unevaluated.

Homoeopathy (Strength of evidence: D, I), using a variety of remedies including calcium, sodium and sulphur has shown no benefit over placebo.⁸

Hypnosis has been evaluated in a double-blind, placebo-controlled trial of 40 individuals treated over 6 weeks. The hypnosis-treated group lost more warts than individuals treated either with topical salicylic acid or with placebo.⁴⁷

Local heat treatment has been tested in 13 patients. Of 29 treated warts, 86% cleared while 41% of placebo-treated warts regressed.⁴⁸

Intralesional interferon has shown some effect in cutaneous warts in a limited number of open trials.⁴⁹

Topical imiquimod applied in a 5% cream for 9–11 weeks has been used in a small number of patients, including immunosuppressed individuals, with encouraging results.^{50,51}

Irradiation, once used quite frequently, now has no place in the management of this benign condition.

Potential audit points

1 Liquid nitrogen cryotherapy – is the treatment regimen used in accordance with recommended frequency, duration, etc., and what is the clearance rate?

2 Topical salicylic acid – is the treatment used in a regimen most likely to produce an effect and what is the clearance rate?

Appendix 1

Strength of recommendations

A There is good evidence to support the use of the procedure

B There is fair evidence to support the use of the procedure

C There is poor evidence to support the use of the procedure

D There is fair evidence to support the rejection of the use of the procedure

E There is good evidence to support the rejection of the use of the procedure

Appendix 2

Quality of evidence

I Evidence obtained from at least one properly designed, randomized trial

II-i Evidence obtained from well designed control trials without randomization

II-ii Evidence obtained from well designed cohort or case control analytic studies, preferably from more than one centre or research group.

II-iii Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence.

III Opinions of respected authorities based on clinical experience, descriptive studies or reports of expert committees.

IV Evidence inadequate due to problems of methodology (e.g. sample size, or length of comprehensiveness of follow-up or conflicts of evidence).

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