BJD
British Journal of Dermatology

British Association of Dermatologists' guidelines for the management of cutaneous warts 2014

J.C. Sterling,[1] S. Gibbs,[2] S.S. Haque Hussain,[1] M.F. Mohd Mustapa[3] and S.E. Handfield-Jones[4]

[1]Addenbrooke's Hospital, Cambridge University Hospitals NHS Foundation Trust, Hills Road, Cambridge CB2 OQQ, U.K.
[2]Great Western Hospital, Marlborough Road, Swindon SN3 6BB, U.K.
[3]British Association of Dermatologists, Willan House, 4 Fitzroy Square, London W1T 5HQ, U.K.
[4]West Suffolk Hospital, Hardwick Lane, Bury St Edmunds, Suffolk IP33 2QZ, U.K.

Correspondence
Jane Sterling.
E-mail: jcs12@cam.ac.uk

Accepted for publication
14 July 2014

Funding sources
None.

Conflicts of interest
J.C.S. has received travel and accommodation expenses from LEO Pharma (nonspecific) and has been an invited speaker at educational events for Healthcare Education Services (nonspecific).

J.C.S., S.G., S.S.H.H. and S.E.H.J. are members of the guideline development group, with technical support provided by M.F.M.M.

This is an updated set of guidelines prepared for the British Association of Dermatologists (BAD) Clinical Standards Unit, which includes the Therapy & Guidelines (T&G) Subcommittee. Members of the Clinical Standards Unit who have been involved are J.R. Hughes (Chairman T&G), M. Griffiths, A.J. McDonagh, S. Punjabi, D.A. Buckley, I. Nasr, V.J. Swale, C.E. Duarte Williamson, P.M. McHenry, N.J. Levell, T. Leslie, E. Mallon, K. Towers (British National Formulary), R. Davis (British Dermatological Nursing Group), C. Saunders (British Dermatological Nursing Group), A.G. Brian (BAD Scientific Administrator), L.S. Exton (BAD Information Scientist) and M.F. Mohd Mustapa (BAD Clinical Standards Manager).

Produced in 2001 by the British Association of Dermatologists; reviewed and updated 2014.

DOI 10.1111/bjd.13310

1.0 Purpose and scope

The overall objective of the guideline is to provide up-to-date, evidence-based recommendations for the management of infectious cutaneous warts caused by papillomavirus infection. The document aims to (i) offer an appraisal of all relevant literature since January 1999, focusing on any key developments; (ii) address important practical clinical questions relating to the primary guideline objective, i.e. accurate diagnosis and identification of cases and suitable treatment; (iii) provide guideline recommendations, where appropriate with some health economic implications; and (iv) discuss potential developments and future directions.

The guideline is presented as a detailed review with highlighted recommendations for practical use in the clinic, in addition to an updated patient information leaflet [available on the British Association of Dermatologists' (BAD) website, www.bad.org.uk].

1.1 Exclusions

This guideline does not cover anogenital warts, bowenoid papulosis, focal epithelial hyperplasia or seborrhoeic keratoses (sometimes called seborrhoeic warts).

2.0 Stakeholder involvement and peer review

The guideline development group consisted of consultant and specialty trainee dermatologists and an editor of the Cochrane Skin Group. The draft document was circulated to the BAD membership, British Dermatological Nursing Group, Primary Care Dermatological Society, British Kidney Patients Association and Royal Pharmaceutical Society for comments, and was peer reviewed by the Clinical Standards Unit of the BAD (made up of the Therapy & Guidelines subcommittee) prior to publication.

3.0 Methodology

This set of guidelines has been developed using the BAD's recommended methodology,[1] with reference to the Appraisal of Guidelines Research and Evaluation (AGREE II) instrument (www.agreetrust.org).[2] Recommendations were developed for

implementation in the National Health Service using a process of considered judgement based on the evidence. PubMed and the Medline and Embase databases were searched for meta-analyses, randomized controlled trials (RCTs) and non-RCTs, case series, case reports and open studies involving warts, published in the English language from January 1999 to March 2014; search terms and strategies are detailed in the Supporting Information. The Allied and Complementary Medicine Database was also searched for 'warts' with the same time restriction. Additional relevant references were also isolated from citations in the reviewed literature. Each author screened their set of identified titles, and those relevant for first-round inclusion were selected for further scrutiny. Working in pairs, the authors then reviewed the abstracts for the shortlisted references, and the full papers of relevant material were obtained; disagreements in the final selections were resolved by discussion among the entire development group. The structure of the 2001 guidelines was then discussed and re-evaluated, with headings and subheadings decided; different coauthors were allocated separate subsections. Each coauthor then performed a detailed appraisal of the selected literature, and all subsections were subsequently collated and edited to produce the final guideline.

4.0 Limitations of the guideline

This document has been prepared on behalf of the BAD and is based on the best data available when the document was prepared. It is recognized that under certain conditions it may be necessary to deviate from the guidelines and that the results of future studies may require some of the recommendations herein to be changed. Failure to adhere to these guidelines should not necessarily be considered negligent, nor should adherence to these recommendations constitute a defence against a claim of negligence.

5.0 Plans for guideline revision

The proposed revision for this set of recommendations is scheduled for 2019; where necessary, important interim changes will be updated on the BAD website.

6.0 Background

Warts are caused by infection of keratinocytes (the predominant cell type in the epidermis) by human papillomavirus (HPV). The development of epidermal thickening and hyperkeratinization occurs following infection at the basal layer and clonal proliferation, which eventually results in a visible wart, weeks or even months later.

There are over 150 genotypically different types of HPV, with classification based on defined variation of the viral DNA. The majority of common warts are caused by HPV types 1, 2, 4, 27 or 57, and plane warts by HPV types 3 or 10. The HPV types originally identified in epidermodysplasia verruciformis (EV) and their closely related genotypes are also found on the skin, often as subclinical infections, but they can be associated with squamous cell cancer and premalignant dysplasias, especially in cases of immunosuppression.

6.1 Terminology

The term 'warts' includes all morphological varieties of warts and may sometimes be used to name wart-like lesions, such as seborrhoeic keratoses or seborrhoeic 'warts', which are not caused by HPV infection. In this guideline the term 'warts' deals only with warts due to HPV infection. HPV-associated warts are subdivided on anatomical or morphological grounds into (i) common wart (*Verruca vulgaris*); (ii) wart on the sole of the foot, plantar wart (*Verruca plantaris*); (iii) flat wart or plane wart (*Verruca plana*) and (iv) genital wart (*Condyloma accuminatum*).

6.2 Epidemiology and course of infection

HPV can spread from one individual to another by direct contact or via the environment. It is not known exactly how long the infectious virus can persist outside the body, but the related bovine papillomavirus is believed to retain infectivity for months or possibly years,[3] and the same may be true for HPV. Warts are a common skin disease worldwide. Infection is common in childhood, but can occur at any age. Small cohort observational studies have suggested that 5–30% of children and young adults have warts.[4–6]

Warts can persist for years with little or no sign of inflammation. Spontaneous clearance of the infection, firstly with a reduction in size of the wart and then its disappearance, can occur at any time from a few months to years later. Clearance in children can occur after only a few months, with half clear at 1 year and about two-thirds by 2 years.[7] However, warts in adults can be much slower to clear, and persistence for 5–10 years is not uncommon.

7.0 Diagnosis

Diagnosis of common hand and foot warts is usually not difficult. Paring down a wart will often result in pinpoint bleeding as the capillary loops of the elongated dermal papillae are exposed. Warts need to be distinguished either clinically or histologically from other keratotic lesions on the hands or feet, such as actinic keratoses, knuckle pads or, more rarely, squamous cell carcinoma or focal palmoplantar keratoderma. On the feet, corns and calluses or callosities can be confused with warts, but paring and close inspection should allow them to be distinguished. On limbs, other hyperkeratotic lesions such as lichen planus or angiokeratoma may cause confusion, and plane warts may need to be distinguished from lichen planus or thin actinic or seborrhoeic keratoses.

7.1 Complications

Impairment of the immune system, especially cell-mediated immunity, usually results in prolonged duration of warts.

When immune function is severely impaired, for example after organ or bone marrow transplant or due to severe combined immune deficiency, warts may be large, extensive and resistant to treatment. Warts may be the presenting feature of milder immunosuppressed states such as lymphoma, idiopathic CD4 lymphocytopenia or HIV infection, so unusually severe or prolonged warts should prompt consideration of underlying immune deficit.

Papillomavirus infection is also associated with premalignancy and squamous cell carcinomas of the skin. In EV, a familial tendency to develop scaly and plane wart-like keratotic lesions in the teens, which frequently progress to squamous cell cancer in early adult life, is attributed to both a mild immune deficit and increased carriage of certain HPV types. A similar skin condition is seen in long-term immunosuppressed individuals, particularly organ transplant recipients. Individuals with these conditions harbour HPV types causing plane warts, and also those types in the subgroup of beta-papillomaviruses, which have a greater frequency than those found in immunocompetent people.

8.0 Management

8.1 No therapy

Depending on their site and size, warts may be just a minor nuisance. If the affected individual is immunocompetent, then an expectant approach to management is entirely acceptable. Some warts can be uncomfortable or interfere with function, or may be a major cosmetic bother and embarrassment when numerous or on sites such as the face. Under these circumstances, a number of different treatments may be considered.

8.2 Interventional treatment

There are numerous treatments for warts, and whether used singly or in combination they often have little evidence base for their use. Home remedies also abound and may have some reason for potential efficacy. Ideally treatment should not leave scars, although many patients may prefer a permanent scar to a persistent, unsightly and troublesome wart.

There is no antiviral treatment that is specific for HPV, but some of the available therapies interfere with the viral life cycle. The most common approach to treatment is to damage or destroy the infected epithelium. This can also induce cell death and antigen exposure and presentation, thereby potentially inducing an immune response. By reducing epidermal proliferation, or more specifically DNA replication, the wart should become less thick and production of new virus inhibited. Destruction of the virus particles, or virucide, at the surface is effected by a limited number of agents, but such treatments may not affect virus-infected cells in lower epidermal layers. Direct stimulation of the immune system in the locality of the wart could maximize the chance of immunological response to the infected keratinocytes. It is not known how much the immune response contributes to wart clearance after destructive or other inflammatory treatments, but the poor or absent response to treatments in immunosuppressed patients would suggest that it is essential.

Common variations between studies include (i) no distinction being made between common and plane warts; (ii) the participants may include both children and adults; (iii) clearance may be assessed by either cleared warts or clear patients; (iv) various body sites can be included; and (v) treatment comparisons may be between participants, or right–left or wart–wart comparisons within individuals. As few treatments currently used for treating warts have been subjected to large, rigorous trials, the available evidence for a large number of different therapies is discussed in these guidelines. Many trials have used a treatment period of 3–4 months with varying follow-up times. Under these circumstances, the cure rate for placebo-treated warts is of the order of 20–30%.

8.2.1 Destructive treatments

Epidermal damage can be produced by chemical means, such as (a) salicylic acid and others (c–j) below, or by physical means, including (b) cryotherapy and others (k–n) below.

8.2.1.a. *Salicylic acid (level of evidence 1+; strength of recommendation A) (see Appendices 1 and 2).* Salicylic acid (SA) formulations are the most common preparation used in the treatment of viral warts. SA is thought to work by promoting exfoliation of epidermal cells; at high concentrations it is an irritant. These effects are postulated to be able to stimulate host immunity, which may be an additional mechanism of action against warts.

The most commonly used, over-the-counter products are SA paints. These contain SA at concentrations of between 10% and 26% in either a collodion or a polyacrylic base; they are often mixed with lactic acid. Plasters containing 40% SA and ointments containing 50% SA are also widely available; weaker, cream preparations can be made. The latter are sometimes used to treat facial warts, but without trial evidence to confirm efficacy.

The method of application of SA depends on the formulation. For wart paints it is recommended that lesions are abraded or pared down and/or soaked prior to application. Care should be taken when paring to avoid abrading the surrounding normal skin, as this may spread the disease. A study looking at the effect of occlusion found a benefit when using a 17% SA gel with lactic acid.[8] Qualitative research has shown that expectation of cure from SA paints is low, and patients find the treatment difficult due to irritation of the surrounding skin. Compliance with treatments is thought to be poor.[9]

In 2011 a meta-analysis of five studies of 333 patients showed SA (all preparations) to be more effective than placebo. The analysis suggested that warts treated with SA are 1·6 times more likely to clear than those treated with placebo, and that 95% of similar trials would yield a treatment benefit of a 1·15–2·24 times increased chance of clearance [relative risk (RR) 1·60, 95% confidence interval (CI) 1·15–2·24]. A pooled analysis of 16 studies of SA with a total of 813 patients

showed that 337 were cured; the mean cure rate was 49%, with a range of 0–69%. In contrast, placebo had a cure rate of 23% (range 5–73%).[10]

Two important trials published within the last few years[11,12] are included in a recently updated Cochrane review.[13] Bruggink *et al.*[11] studied 250 patients in primary care who were randomized to one of three treatment regimens: SA 40% ointment, fortnightly cotton-bud cryotherapy, or no treatment for 13 weeks. The cure rates for all sites combined were 15%, 49% and 8%, respectively; subgroup cure rates were: hand warts, 17%, 46% and 7%, respectively, and plantar warts, 33%, 30% and 23%, respectively. Thus, in this trial SA was less effective than cryotherapy for the treatment of hand warts, but more effective than no treatment at all. Neither treatment seemed particularly effective for plantar warts. A lack of effectiveness of both SA and cryotherapy for treating plantar warts is also corroborated by data from the trial of Cockayne *et al.*[12] This involved 240 patients with plantar warts treated in U.K. podiatric practices, with either SA 50% for 12 weeks or 'gentle' cryotherapy (up to four treatments delivered by spray or probe usually with prior paring of overlying skin). There was neither a placebo nor a no-treatment group, and both treatments achieved a modest cure rate of only 14%. While these recent studies help confirm the efficacy of SA, there is still a paucity of data on the commonly used formulations of SA paint.

1 *Adverse effects*. All but very low-strength SA can cause chemical burns and should not be used in areas of poor healing such as neuropathic feet.[14] On the face, SA paints are contraindicated due to risk of irritant burning, and this can also occur on other sites.[15] In areas of sensitive skin, 2% SA cream has been used but without any evidence base. Contact allergy to the excipients is also reported.[16]
2 *Combination therapies (level of evidence 2−)*. The most commonly used combination therapy is cryotherapy and SA. In an open study, a clearance rate of 86% (25/29) was reported in a retrospective analysis of cases treated with both cryotherapy and SA 70%.[17] There were uncontrolled variables in this study: the number and frequency of cryotherapy treatments was decided by the practitioner and the follow-up period was up to 4·5 years.

In a study of 10 patients with 66 warts, the application of SA 30% prior to pulsed-dye laser (PDL) therapy appeared to decrease the number of laser treatments needed, but while the study was randomized, it was a single-blinded trial and involved within-patient comparisons.[18] In an open study, diphencyprone (DPC) 0·1% was combined with SA 15% ointment in a trial of 50 patients with palmoplantar warts and applied for up to 4 months. The combination showed a 92% clearance in those completing the treatment, with 88% clearance in intention-to-treat cases.[19]

SA (either 17% or 40%) has also been combined with 5-fluorouracil (5-FU, either 0·5% or 5%) for plantar warts, with 100% resolution; however, the regimens were complex and treatment continued for up to 235 days in one patient.[20]

SA has also been compounded with podophyllotoxin and cantharidin, and used on plantar warts, clearing 95·8% of patients (138/144), with 86·8% (125/144) needing only a single application. However, application was complex, and blistering and pain could result.[21]

8.2.1.b. Cryotherapy (level of evidence 1+; strength of recommendation B). A range of devices and techniques are used to induce targeted cold injury to warts. Liquid nitrogen, delivered by cryospray or cotton bud, is the most commonly used method in medical practice. Compressed-gas devices containing propane and dimethyl ether can be purchased without prescription but do not achieve temperatures as low as liquid nitrogen and are therefore likely to be less effective,[22,23] although there is one randomized trial suggesting that they are equally effective.[24]

Techniques differ between practitioners, with variations in freeze times, mode of application and intervals between treatments. Paring before cryotherapy can improve results in plantar warts, but not hand warts.[25] It is common practice to freeze until a halo of frozen tissue appears around the wart, and this is maintained for 5–30 s depending on the site and size of the wart. Standard practice is to repeat the treatment every 2–3 weeks until the warts have cleared, up to a maximum of approximately six treatments. The available evidence from randomized trials broadly supports this, except in the case of plantar warts where no treatments, including cryotherapy, have been convincingly demonstrated to be consistently and significantly effective.

Two trials of cryospray vs. cotton-bud cryotherapy (one RCT and one controlled trial) showed the techniques to be of equivalent effectiveness.[26,27] Cotton-bud application is probably preferable when treating warts on the face in children; an alternative technique is to freeze the tips of a pair of forceps and then grip the wart.[28,29]

The reported cure rate of cryotherapy for warts at all sites from randomized trials is highly variable, ranging from 0% to 69% with a mean of 49%.[10] Where possible, subgroup analysis of data from these trials suggests that cure rates are generally better for hand warts than for plantar warts. Two recently published trials[11,12] have provided much better-quality data than previously and have compared cryotherapy directly with SA.[13] As discussed in the section on SA (section 8.2.1.a.), cryotherapy gave equivalent or improved rates of cure when compared with SA.

More aggressive cryotherapy with a longer freeze or a double freeze–thaw cycle appears to be more effective than gentler freezing, but the evidence is very heterogeneous and the data are not of very high quality.[30–33] Not surprisingly, more intense cryotherapy also tends to result in more pain and blistering and with an increased risk of scarring. The study by Berth-Jones *et al.*[32] is often cited, but it had a very high dropout rate (31%), making the apparent advantage of the double freeze–thaw cycle for plantar warts (an improved cure rate of 65% vs. 41%) rather less convincing. The study by Connolly *et al.*[33] (with a 22% dropout rate) showed that a longer freeze time (10 s sustained vs. a 'traditional' freeze) improved cure

rates at all sites (64% vs. 39%), but the number of patients with plantar warts was too small for subgroup analysis.

In trials comparing the interval between treatments, most, but not all, have suggested that freezing every 2–3 weeks produces a better clearance at 3 months than treatment every 4 weeks.[34–37] However, the cure rates after 6 months are often similar, suggesting that clearance may in fact depend on the total number of treatments given. Only one randomized trial has explored the total number of treatments, and even this trial was not ideally designed to answer this question. There was also a high dropout rate (19% in the first part of the trial and 26% in the second), introducing a considerable risk of bias. In a mixed population of 155 patients with persistent warts at all sites that had not cleared after 3 months of 3-weekly cryotherapy treatments (about four treatments), there was no demonstrable benefit shown after a further 3 months of treatment.[25]

Patients should be warned that cryotherapy is painful and blistering may occur. Adverse effects are more frequently reported in shorter-interval treatment regimes. Caution must be used when applying cryotherapy near cutaneous nerves, tendons and the nail apparatus, and also in patients with impaired arterial or venous circulation. Hypopigmentation or hyperpigmentation may occur, particularly in patients with darker skin types.

8.2.1.c *Silver nitrate (level of evidence 2−).* A silver nitrate 10% solution was investigated in a placebo-controlled, double-blinded study of hand and foot warts in 60 children and adults, and showed a clearance rate of 63% of patients after 6 weeks.[38] However, the data shown relate only to the response to the silver nitrate, with no data given for the placebo, making interpretation impossible. Yazar and Başaran studied the effect of silver nitrate pencils and reported a cure rate of 43% of patients in the treatment group and 11% with placebo.[39]

8.2.1.d. *Phenol (level of evidence 2+; strength of recommendation D).* Phenol is a caustic agent that has been compared with cryotherapy in a single-blinded, randomized study of 60 patients with hand warts. Cryotherapy was applied weekly with a cotton stick for 10–20 s, and 80% phenol was applied weekly. The cure rates of patients were 70% with cryotherapy and 83% with phenol, although the dropout rate with phenol was higher.[40]

8.2.1.e. *Cantharidin (level of evidence 3; strength of recommendation D).* This is a blistering agent that triggers acantholysis. The superficial nature of the injury reduces the risk of scarring. It also has the advantage of painless application, with discomfort developing only when blistering occurs in the 24 h following application. A study of 15 patients who were treated with a cantharidin 0·7% solution to treat plane facial warts showed clearance of warts in all 15 patients within 16 weeks with one to four treatments.[41] Taken systemically it is highly toxic.

8.2.1.f. *Glycolic acid 5% (level of evidence 3; strength of recommendation D).* Glycolic acid is an α-hydroxy acid that acts as a peeling agent. In a case series of 15 children with facial plane warts it was well tolerated, cleared all of the cases and did not produce scarring. However, spontaneous resolution may have occurred, especially in one case that did not clear until after 4 months.[42] An open study of SA 2% combined with glycolic acid 15% in 20 patients aged 7–16 years with recalcitrant facial flat warts reported a 100% cure rate within 8 weeks.[43]

8.2.1.g. *Pyruvic acid (level of evidence 3; strength of recommendation D).* Pyruvic acid is used as a peeling agent. In a case series investigating the response of common warts to pyruvic acid 70% alone or in combination with 5-FU 0·5%, 80% of patients showed improvement. The addition of 5-FU did not increase the effect.[44] Hypertrophic scarring was reported in a patient using pyruvic acid 98% with 5-FU 2% for warts on the chest and arms.[45]

8.2.1.h. *Citric acid 50% (level of evidence 2−).* Citric acid was compared with tretinoin in a prospective randomized, double-blinded study of 75 patients with plane warts on the body. The study design used a side-to-side comparison and the results were given as number of warts cleared. After 6 weeks 64% of citric acid-treated lesions were cleared, vs. 54% of the tretinoin-treated lesions.[46]

8.2.1.i. *Formic acid (level of evidence 2−).* Formic acid is another low-cost treatment. As an acid, it is stronger than SA but weaker than trichloroacetic acid. A number of studies have suggested its efficacy.[47–49] Side-effects are common, with 12% of participants in one study developing an infection and needing systemic antibiotics.[47]

8.2.1.j. *Trichloroacetic acid and monochloroacetic acid (level of evidence 3; strength of recommendation D).* These caustic agents have been used to treat warts. Trichloroacetic acid is used regularly to treat genital warts,[50] and has been used without adequate trial evidence to treat common warts.[51] Monochloroacetic acid showed a success rate of 61%, and the addition of formaldehyde had no effect on the response rate.[52] Monochloroacetic acid is highly toxic and corrosive.[53]

8.2.1.k. *Hyperthermia (level of evidence 2+; strength of recommendation D).* Two randomized trials have studied the effects of localized heat on warts.[54,55] The more recent trial involved 60 patients with plantar warts randomized to hyperthermia with red light (up to 44 °C for 30 min on three consecutive days) or placebo red light alone. Cure of treated lesions occurred in 54% (15/28) vs. 12% (three of 26) of patients, respectively (RR 3·37, 95% CI 1·05–14·18).[55] The earlier randomized trial,[54] involving 13 patients with hand warts and using warts as the unit of analysis, and a case series[56] are less rigorous studies, but also suggest that localized hyperthermia can be effective and is reasonably safe.

8.2.1.l. *Surgical interventions (level of evidence 3; strength of recommendation D)*. There are no high-quality studies published on the effectiveness of surgical treatments such as curettage, cautery and CO_2 laser, although these treatments are certainly widely used. One case series of 50 patients treated with 2–4-MHz electrowave 'electrosection' (an accurately targeted destructive treatment using radio waves rather than heat) claimed a 67% success rate with solitary plantar warts and commented that relapse was more common in warts that occurred at weight-bearing sites.[57]

8.2.1.m. *Lasers (level of evidence 2+; strength of recommendation C)*. PDL (585 nm) is the laser used most frequently and acts by destroying wart vessel vasculature through haemoglobin's absorption peak at 585–595 nm. Direct thermal injury to the heat-sensitive HPV virus may also play a role. Treatment protocols (pulse width, fluence, spot size, number of pulses and duration of treatment) vary between studies, making efficacy difficult to evaluate. One RCT found no significant difference in outcome between groups treated with PDL, cryotherapy or cantharidin.[58] Cohort studies have reported patient clearance rates with PDL of 32–75%,[59–61] and a case series of 142 patients with over 700 warts reported 93% clearance of treated warts after an average of 2·5 treatments.[62]

Most warts are pared down before PDL to facilitate absorption of the laser energy. Pretreatment with SA 30% for 5 days, followed by PDL, led to faster complete clearance (2·2 sessions in the SA-PDL group vs. 3·1 sessions in the PDL-only group, $P < 0{\cdot}05$), with similar proportions of patients responding to treatment overall.[18]

Two studies using PDL followed directly by intralesional bleomycin led to 60–89% wart clearance, including 80% clearance in immunosuppressed patients.[63,64] Wart location and duration may influence the rate of clearance. Palmar and periungual warts are cleared more effectively than plantar warts.[60,61,65]

The main side-effects of PDL include local pain (although generally not severe enough to warrant stopping treatment), haemorrhagic bullae, pigmentary change and scarring. PDL is well tolerated by children, with two large cohort studies reporting complete response in 48% of treated warts[66] and 75% of children with palmoplantar warts.[61]

CO_2 laser, neodymium-doped yttrium aluminium garnet (Nd:YAG), Er:YAG, infrared and potassium titanyl phosphate laser have also been used in a small number of cohort studies. The largest of these reported a 96% clearance rate of recalcitrant common, palmoplantar and periungual warts in 369 patients treated with Nd:YAG laser.[67]

8.2.1.n. *Photodynamic therapy (level of evidence 2+; strength of recommendation D)*. There was a significant difference in wart clearance after 14 weeks in 45 patients with palmar and plantar lesions treated with 20% aminolaevulinic acid photodynamic therapy (ALA-PDT) (50 mW cm^{-2}, 23-min treatment time, 70 J cm^{-2}, six treatments maximum) compared with placebo-PDT. However, patients also applied a keratolytic ointment (SA and lactic acid) between PDT treatments.[68] In total, 75% of plantar warts completely resolved in 67 ALA-PDT-treated patients (50 mW cm^{-2}, 50 J cm^{-2} visible light irradiation, three treatments maximum) compared with 23% in the placebo group. Both groups received urea 10% and SA 10% ointment for a week prior to commencing treatment.[69]

Cohort studies have reported clearance rates of warts between 58% and 95%.[70–72] PDT can be used in combination with laser; in such a study, 12 patients with periungual warts treated with CO_2 fractional laser followed by methyl-5-aminolaevuninic acid (MAL)-PDT (3 h, 50 J cm^{-2}, 15 min, fortnightly treatments over 6 weeks) resulted in 90% of treated warts clearing completely with no recurrence in 6 months.[73] In another study, 19 patients with hand and foot warts were treated with MAL-PDT plus a PDL light source, which cleared 53% of treated warts; hand warts cleared more effectively than plantar warts.[74]

As with laser treatment, it is difficult to compare efficacy rates in published papers due to variation in PDT regimens, for example the duration of application of topical photosensitizers, the type of light source used, fluorescence and the number of treatments. Many studies prepare warts before treatment, with curettage, blunt scraping, scalpel or keratolytic cream to enhance penetration. Azone, a topical penetration enhancer, has been used before PDT in two studies, with 83% clearance of plantar wart[75] and 94% clearance of *V. plana* on the face.[76] For facial plane warts, a reduction in concentration of ALA from 20% to 10% can maintain efficacy but reduce the chance of post-treatment hyperpigmentation.[77]

8.2.2. Virucidal agents

8.2.2.a. *Formaldehyde (level of evidence 3; strength of recommendation D)*. Formaldehyde soaks have been used to treat verrucas, and they were reported to give a cure rate of 80% in an open study of 646 children.[78] This study applied 3% soaks to pared plantar warts. If the skin hardened, the concentration was increased to a 10% solution. Formaldehyde is also available as a 0·75% gel. No randomized study has been completed. Formaldehyde is allergenic.

8.2.2.b. *Glutaraldehyde (level of evidence 3; strength of recommendation D)*. A glutaraldehyde 10% paint was reported as being equivalent to SA paint in plantar warts.[35] A series of 25 patients with resistant warts showed a cure rate of 72%, and the treatment was well accepted in children.[79] Reports of deep necrosis demonstrate the risk of repeated application, and glutaraldehyde should be used with caution especially in concentrations > 10%.[80]

8.2.3. Antiproliferative agents

8.2.3.a. *Vitamin D analogues (level of evidence 3; strength of recommendation D)*. There are three case series[81–83] and two case reports[84,85] on the use of vitamin D analogues for treatment of warts. The largest case series, by Inaba *et al.*,[82] reported

complete regression of warts in 59% of patients (13/22; all ages, all sites) treated with maxacalcitol and occluded with SA plasters for up to 45 days.

8.2.3.b. *Dithranol (level of evidence 2−).* One small RCT of dithranol 2% cream vs. Verucid® (11% SA, 4% lactic acid with copper), showed a higher cure rate for dithranol: 56% (15/27) vs. 26% (eight of 31).[86] Three case series showed patient cure rates of 60–70%.[87–89] In the series of Hjorth *et al.*,[87] 71% of patients (17/24) were cleared of mosaic plantar warts within 10 months of daily treatment with dithranol 2%.

8.2.3.c. *Podophyllin and podophyllotoxin (level of evidence 3; strength of recommendation D).* Podophyllotoxin can inhibit cell division by interfering with the mitotic spindle, and will affect normal skin as well as warts. It can have dangerous systemic effects if used in high concentrations or over large areas, and its use is contraindicated in pregnancy. Although podophyllotoxin (and previously the cruder podophyllin) is a standard treatment for anogenital warts, its evaluation in cutaneous warts has been limited. The assumption is that penetration of the thick, cornified layer of cutaneous warts is poor compared with that achieved at mucosal sites. A very small open study of 40 patients with plantar warts treated with podophyllin 25% in liquid paraffin under prolonged adhesive plaster occlusion reported a 67% clearance rate of patients at 3 months.[90] However, the side-effects of this treatment include an intense inflammatory reaction with blistering, which can be very painful. There are no recent studies using podophyllotoxin for cutaneous warts, except as a 1% component of a combination therapy with cantharidin and SA, so the contribution of podophyllotoxin alone is impossible to evaluate.[91]

8.2.3.d. *5-Fluorouracil (level of evidence 2+; strength of recommendation C).* Topical 5-FU has been used with effect to treat both plane warts and common warts on the hands and feet. 5-FU blocks DNA synthesis and damages dividing basal layer cells. When used topically or intralesionally, it produces inflammation and occasionally erosions. Hyperpigmentation, or less frequently hypopigmentation, can occur if it is used for longer periods.

In one study, 5-FU 5% cream was applied once a day for 4 weeks under occlusion to hand or foot warts on one side of the body, while a placebo cream was simultaneously applied to warts on the other side of the body. At the end of the treatment, 60% of warts were cleared on the side treated with 5-FU compared with 17% on the placebo-treated side.[92] In a similarly designed study, treating adult plantar warts for 12 weeks led to complete clearance in 95% of patients (19/20), with 10% clearance in the placebo arm.[93] In a small open study, application of the cream to plane warts twice a day led to similar clearance rates.[94]

Topical 5-FU under occlusion was more effective than occlusion alone in an unblinded RCT of 40 patients. In total, 95% of patients using 5-FU under occlusion cleared their warts compared with 10% in the control group.[93] There was no difference in outcome when 5-FU was used in combination with cryotherapy vs. cryotherapy alone.[95]

5-FU has been used in a weak preparation (0·5%) in combination with SA (10%). In a meta-analysis, the combination appears much more effective than SA alone (63·4% clearance vs. 11%).[96]

In a double-blinded RCT, 65% of warts in 40 patients cleared with up to four injections, given weekly, of intralesional 5-FU 4% (in combination with lidocaine and adrenaline) compared with 35% in the placebo group ($P < 0{\cdot}05$).[97] Isçimen *et al.*[98] reported a 70% complete clearance of warts in a similar single-blinded RCT.

8.2.3.e. *Bleomycin (level of evidence 2+; strength of recommendation C).* Bleomycin is a cytotoxic agent used in systemic chemotherapy, but it has been recognized and applied as a therapy for warts for 40 years.[99] Bleomycin solution can be injected into warts using a small needle and syringe, or applied to the surface and 'pricked' into the wart with a needle. The strength of bleomycin used has usually been 1 U mL^{-1}, equivalent to 1 mg mL^{-1}, but weaker strengths of 0·5 mg mL^{-1} or even 0·1 mg mL^{-1} seem to produce similar effects.[100,101] The introduction of bleomycin into the skin is painful, and local anaesthesia, either before or together with administration of bleomycin, helps to make the procedure more comfortable. The effect of bleomycin on the wart produces some pain that lasts a day or two, and then necrosis develops with a black eschar that separates after a few days. This obvious response to treatment makes it difficult to conduct double-blinded trials, and many studies have been open studies or have used bleomycin in comparison with saline injection or cryotherapy.

Open studies have suggested clearance rates of approximately 20–90% of treated warts with one or more treatments,[101,102] with most reporting a patient response rate of approximately 65–85%.[101,103]

Several trials of intralesional bleomycin have used saline as a placebo. In one study where 25 patients were allocated to each treatment, 96% (82/85) of warts treated with bleomycin cleared, while only 11% of warts (eight of 72) treated with saline showed clearance at 3 months.[104] A smaller study, in which 24 patients with multiple warts had one wart treated with bleomycin and a similar wart injected with saline (control), reported a comparable clearance, with 58% of bleomycin-treated warts clearing compared with only 11% of the control warts.[105]

When compared with cryotherapy, and using one body side for each treatment, bleomycin produced higher clearance rates (92–97% of bleomycin-treated warts vs. 76–82% of warts treated with cryotherapy).[106,107]

The major side-effect of bleomycin is pain at the time of injection and for up to 48 h afterwards. Flagellate hyperpigmentation, which may occur with standard systemic chemotherapy, has also been reported,[108] as has postinflammatory pigmentation, which usually clears after some weeks.[109]

8.2.3.f. *Retinoids.*

1 *Topical retinoids (level of evidence 2+; strength of recommendation C).* Retinoids affect epidermal proliferation and differentiation and so can reduce wart volume and alter stratum corne-

um quality and quantity. Their main side-effect, both from topical and systemic administration, is skin dryness and skin irritation, which could influence inflammatory reactions in the skin and contribute to the drug's immunomodulatory effects. In spite of ease of access and availability, there are very few reports of the use of topical retinoids in the treatment of warts. Two small studies assessing plane warts in children[110] and organ transplant patients[111] have suggested 85% clearance (compared with 23% untreated) or 29% lesion clearance (compared with 19% placebo treated), respectively, after 6–12 weeks of treatment with tretinoin 0·05% cream. Adapalene 0·1% gel applied under occlusion for 1 week has also been used, but proper evaluation is lacking.[112]

2 *Systemic retinoids (level of evidence 3; strength of recommendation D).* There are many anecdotal reports of oral retinoid use in severe warts, including in immunosuppressed patients. The effect of acitretin 0·5–1 mg kg^{-1} per day for up to 3 months is usually a reduction in the bulk of lesions, but with a high risk of recurrence on discontinuation of therapy.[113] In an observational study of children aged 2·5–12·5 years treated with oral etretinate for 3 months, 80% (16/20) were clear of all warts at 1 year after follow-up.[114] An open study of child and adult patients with facial plane warts reported 73% clearance after 2 months of treatment with isotretinoin 0·5 mg kg^{-1} per day.[115]

8.2.3.g. *Cidofovir (level of evidence 3; strength of recommendation D).* Cidofovir is a potent nucleoside analogue that competitively inhibits DNA polymerase and therefore prevents replication of cidofovir-incorporated viral cells.

Several case reports have supported the use of intravenous cidofovir in immunosuppressed patients,[116–120] but it is generally used topically. Topical cidofovir is reconstituted from the parenteral form, as either a 1% or 3% cream. It is applied under occlusion for 5 days of the week followed by no treatment for a week; this cycle can then be repeated.

Cidofovir 1% cream was used to treat long-standing warts in a case series of seven children, with four achieving complete clearance after 8 weeks of treatment, lasting up to a year in 75% of cases.[121] A child with acute lymphocytic leukaemia applied cidofovir 1% cream to a painful plantar wart daily for 6 weeks leading to complete resolution.[122] Cidofovir can also be used intralesionally, and with an average of 3·2 injections, clearance of 98% of warts has been reported in an open study.[123]

Side-effects of intravenous cidofovir include nephrotoxicity, neutropenia and metabolic acidosis. Topical cidofovir appears to be well tolerated other than causing local irritation, although one patient with a background of chronic renal failure developed acute deterioration in renal function during treatment.[123,124]

8.2.3.h. *Occlusotherapy (level of evidence 2−).* The use of occlusion for treatment of cutaneous warts has been practised for some time, with a suggestion of 47% of patients cleared at 2 months,[90] but the first trial of its use was not reported until 2002.[125] A single wart in each of 61 children was treated with either light cryotherapy (10 s of liquid nitrogen every 2–3 weeks) or common silver duct tape applied and left in place for 1 week for a total of 8 weeks. In total 60% of the cryotherapy-treated warts cleared, compared with 85% of the warts treated with duct tape. Two further trials have used transparent duct tape applied to a single wart for up to 8 weeks, but without a statistically increased rate of clearance. In a trial involving 100 children randomly allocated to either duct tape over the wart or a ring-shaped corn pad around the wart, 16% of warts cleared in the treatment group compared with 6% in the placebo group.[126] In a study of 90 adults treated with the same tape, again applied weekly for up to 8 weeks, and compared with adhesive-backed moleskin padding, clearance rates were approximately 20% in both groups.[127] Although these studies have not confirmed a definite effect of occlusion on warts, there is the possibility that an effect may occur in children. Many other topical treatments for warts may include some form of occlusion, and the role of this part of treatment is yet to be clarified.

8.2.4. Immunological therapy

8.2.4.a. *Imiquimod (level of evidence 3; strength of recommendation D).* Imiquimod is a well-established treatment for genital and perianal warts. It stimulates a proinflammatory response through the induction, synthesis and release of interferon (IFN)-α, tumour necrosis factor-α and interleukin (IL)-12, as well as promoting natural killer (NK) cell activation. There are no RCTs studying the effect of imiquimod on cutaneous warts. However, two open-label studies have shown > 50% clearance of warts, firstly in 76% of patients when imiquimod was applied twice daily for a maximum of 24 weeks,[128] and secondly in 56% of 50 patients, of whom 19 were immunosuppressed, after 9·5 weeks of treatment.[129] Application under occlusion does not appear to enhance the efficacy.[130] There are numerous case reports reporting the effectiveness of imiquimod in both immunocompetent and immunocompromised patients.[131,132] It has a tolerable side-effect profile with mild-to-moderate local pain reported most frequently.

8.2.4.b. *Contact immunotherapy (level of evidence 2+; strength of recommendation C).* Contact immunotherapy with diphenylcyclopropenone/diphencyprone (DPC) or squaric acid dibutyl ester (SADBE) induces a local delayed hypersensitivity reaction at the wart site triggering a local immune response.

An 8-year retrospective review of 48 patients with palmoplantar warts treated with DPC reported 88% complete clearance of all warts. The median treatment time was 5 months, and no recurrences were observed in a 2-year follow-up period.[133] A similar review of treatment over 7 years reported an 87·7% complete response rate.[134] Although the clearance rate is reduced in immunosuppressed patients, sensitization is possible and this treatment can be effective.[135]

Of 443 adults and children who completed treatment with SADBE twice weekly for a maximum of 10 weeks, 86% underwent complete resolution and 13·8% showed no response to the contact sensitizer. All plantar warts responded, but statistical analyses to identify whether the wart site was a significant variable was not undertaken.[136] A retrospective review has suggested that topical trichloroacetic acid 50% in combination with SADBE immunotherapy can enhance clearance rates.[137]

Side-effects of SADBE and DPC include erythema, desquamation, oedema, pruritus and mild burning. A small number of patients may develop autoeczematization or widespread urticaria, and treatment should be stopped in these cases.

Other allergens including products used for immunization, such as bacille Calmette–Guérin (topical) or measles vaccine (intralesional), have been proposed as useful therapies. Topical therapies may have particular use for children and for the treatment of plane warts.[138]

8.2.4.c. *Intralesional immunotherapy (level of evidence 1−).* Intralesional *Candida*, mumps and tuberculin antigens have been used to induce wart clearance through antigenic stimulation of the host-cell-mediated immune system. There is no robust evidence to support the use of this type of intralesional immunotherapy, but reported clearance rates range from 47% to 87%. A single-blinded RCT of intralesional *Candida* and IFN-α showed that patients receiving the antigen were more likely to respond, but that the addition of IFN did not significantly alter the response rate.[139]

Phillips *et al.*[140] retrospectively reviewed 149 adults and children treated with *Candida* immunotherapy. Within 8 weeks of completing treatment, 72% of patients had achieved complete wart clearance. However, a separate review of 277 patients comparing *Candida* antigen with 'traditional therapy' (including cryotherapy and SA) found no significant difference in outcome between the different groups.[141]

8.2.4.d. *H2 receptor antagonists (level of evidence 1−).* H2 receptor antagonists are widely used in the treatment of gastro-oesophageal reflux. They increase IL-2 and IFN-γ expression from T lymphocytes, enhancing cell-mediated immune responses. The efficacy of cimetidine has been demonstrated in open-label studies: high-dose cimetidine (30–40 mg kg^{-1} per day) was more effective at clearing warts than low-dose cimetidine (20–30 mg kg^{-1} per day),[142] and 87% of children who received cimetidine for 3 months had complete resolution of their warts.[143] However, these results have not been replicated in RCTs, which have found no statistically significant difference between cimetidine and placebo.[144,145]

Ranitidine, which does not have antiandrogenic activity (as opposed to cimetidine), has been investigated in one open-label study. In total 49% of patients with multiple common or plane warts completely responded to a 4-month course of ranitidine 300 mg twice daily, with no recurrence in a 6-month follow-up period.[146]

8.2.4.e. *Other systemic immunotherapy (level of evidence 3; strength of recommendation D).* Single-patient case reports have described good outcomes with IFN,[147] immunoglobulin[148] and valaciclovir[149] in immunosuppressed patients with warts.

8.2.4.f. *Zinc oxide and zinc sulfate (level of evidence 1−).* The mechanism of action of zinc in the treatment of warts is uncertain. Zinc is important for immune regulation and mediates the role of leucocytes and NK cells. Zinc deficiency causes lymphopenia, and can manifest as acrodermatitis enteropathica. Zinc can be used topically or systemically, but there are no robust data to support its use in the treatment of warts.

A double-blinded RCT showed no difference between oral zinc sulfate and placebo.[150] A poor-quality single-blinded RCT showed 87% response in the zinc sulfate patient group, compared with no response in the placebo group, but all patients had a low serum zinc level pretreatment.[151] Yaghoobi *et al.*,[152] who have also published results of a pilot study,[153] reported a 78% response with similar doses of zinc.

Gastrointestinal side-effects including nausea, vomiting and abdominal pain occur frequently, although they do not always necessitate withdrawal of treatment in the published studies.

Topical zinc sulfate 10% is more effective than zinc sulfate 5% or placebo in the treatment of common and plane warts, with 86% complete clearance achieved vs. 10% clearance in the placebo group.[154] In a double-blinded RCT of zinc oxide 20% vs. an SA/lactic acid ointment, 50% of patients achieved clearance in the zinc oxide group compared with 42% in the SA/lactic acid group.[155] It is a simple and safe treatment but has not been compared with placebo.

8.2.5. Complementary and alternative treatments

Most cultures have a history of charms, herbal treatments and other remedies for warts.[156,157] Modern complementary therapies are often derived from these treatments. They can be divided as follows: (i) psychological treatments, e.g. hypnosis; (ii) herbal treatments; (iii) homeopathic treatments; and (iv) acupuncture.

8.2.5.a. *Psychological treatments for warts (level of evidence 2−).* In many people warts resolve spontaneously within 8 months, so it is therefore very difficult to know whether there is an additional effect from suggestion or not.[157]

Hypnosis is the most studied technique and can be subdivided into direct suggestion and visual imagery. A randomized study comparing hypnosis with SA, control (no treatment) and placebo (base carrier from SA) showed a greater effect with hypnosis, but the numbers were small with only 10 patients per group.[158] Studies attempting clearance of warts from one-half of the body and not the other have shown conflicting results.[159,160] However, this has to be viewed in the light of a paper showing that when warts were treated with CO_2 laser on one side of the body the warts on the other side also cleared.[161]

A study of 97 patients treated with distant healing showed no effect.[162] A more elaborate form of suggestion utilized simulated X-ray therapy; however, while the report suggested that the treatment was successful, only 55% of children (five of nine) showed clearance in 2 months.[163]

8.2.5.b. *Herbal treatments (level of evidence 2−).* The destructive effect of caustic sap has been exploited to treat warts, but burns can result. Plants used include mayapple (*Podophyllum peltatum*) (the source of podophyllin) and greater celandine (*Chelidonium majus*).[164] Garlic (*Allium sativum*) was shown to have effect against warts in a study of an extract from garlic, but while there was a control group the study does not appear to have been randomized.[165] Pure garlic can cause skin irritation. The sap from figs was compared with cryotherapy in a 'left–right' comparison; 44% (11/25) of warts cleared with fig sap vs. 56% (14/25) with cryotherapy. While the study had design flaws, fig sap was free of side-effects and is inexpensive in some parts of the world.[166] A study compared oral treatment with propolis (45 patients) with *Echinacea* (40 patients) and placebo (50 patients). Clearance was seen in 18, six and four patients, respectively. The dropout rate was high and

Table 1 Summary of recommended treatments for hand warts

Strength of recommendation	Treatment	Suggested method of use for hand warts
A	Salicylic acid (SA)	Topical preparations of 15–26% SA, applied daily after removing thick keratin layer, with occlusion if possible. Continue for 3–4 months[11,35]
B	Cryotherapy	Keep wart frozen for 15–30 s, repeating every 2–4 weeks for at least 3 months or six treatments[11,35]
C	Bleomycin	A 0·1–1 U mL^{-1} (0·1–1 mg mL^{-1}) solution injected or pricked into wart after local anaesthesia – one to three treatments. Painful during and after treatment[101,102]
	Contact immunotherapy	After initial sensitization, DPC or SADBE at strength appropriate for patient, applied from twice weekly to every 3 weeks for 3–6 months[133,134]
	5-Fluorouracil	A 5% cream applied daily + occlusion for 4–12 weeks[92,93]
	Laser	Pulsed-dye laser after paring and/or SA pretreatment. Two to four treatments at 7–10 J cm^{-2} are usually needed[59–61]
D	Acupuncture	Auricular acupuncture weekly for 10 weeks[171]
	Cantharidin	A 0·7% solution applied every 3 weeks up to four times[41]
	Cidofovir	A 1% cream daily for 5 days each week under occlusion for 8 weeks[121,122]
	Formaldehyde	A 3–4% solution as a daily 15–20-min soak for plantar warts, with emollient protection of unaffected skin for up to 8 weeks[78]
	Glutaraldehyde	A 10% solution applied daily after paring or rubbing down for 3 months[79]
	Hyperthermia	Heat wart(s) to 40–44 °C for 30 min on three to five consecutive days[55,56]
	Imiquimod	A 5% cream twice daily for up to 6 months[128]
	Phenol	An 80% solution applied weekly for up to 6 weeks[40]
	Photodynamic therapy	ALA-PDT after paring and/or SA pretreatment, up to three treatments[71]
	Podophyllin	Podophyllin but not podophyllotoxin tested. After paring or rubbing down. 25% in liquid paraffin applied under occlusion.[11] Authors advise weaker strength (10–15%) and cautious use[90]
	Pyruvic acid	A 70% solution applied daily for up to 2 months[44]
	Retinoids, systemic	Acitretin 0·5–1 mg kg^{-1} per day for up to 3 months[113]
	Surgery	Curettage, cautery, or hyfrecation for filiform warts
	Trichloroacetic acid	Trichloroacetic acid 50–80% solution applied weekly for up to 8 weeks
	Vitamin D analogues	Maxacalcitol three times a day for 2–6 months, with or without SA plaster[82,83] Calcipotriol once daily for 2–3 months[84]
Insufficient evidence	Citric acid	Although they may be used in practice, further study is needed before these can be recommended
	Dithranol	
	Formic acid	
	H2 receptor antagonists	
	Herbal treatment	
	Homeopathy	
	Hypnotherapy	
	Intralesional immunotherapy	
	Occlusotherapy (e.g. duct tape)	
	Retinoids, topical	
	Silver nitrate	
	Zinc oxide	
	Zinc sulfate	

DPC, diphencyprone; SADBE, squaric acid dibutyl ester; ALA-PDT, aminolaevulinic acid photodynamic therapy.

analysis was not done using intention to treat, so the positive effect may have been overestimated.[167] One study used smoke from burning the leaves of *Populus euphratica*; in this single-blinded study of 60 patients, smoke was directed into a box-like structure surrounding the limb. The effect was compared with cryotherapy. While the smoke showed a positive effect, the method of administration could have had a mild thermal or placebo effect.[168]

8.2.5.c. *Homeopathy (level of evidence 1−).* Homeopathy has many opponents and the use of extreme dilution of a substance that, undiluted, causes the symptoms that are being treated has no scientific explanation to date. However, it is probably safe unless the remedy is contaminated. A randomized placebo-controlled study of 60 children using individualized remedies showed no effect in comparison with placebo; however, the method of use of homeopathy was criticized.[169,170]

8.2.5.d. *Acupuncture (level of evidence 2+; strength of recommendation D).* While there are only isolated case reports showing an apparent effect of acupuncture for common warts, there is a single-blinded randomized study of auricular acupuncture for plane warts. The study compared acupuncture with tretinoin 0·1% ointment. In total 53% (16/30) of patients treated with acupuncture cleared, compared with 3% (one of 30) in the tretinoin group.[171]

8.2.6. Other treatments

There are single case reports of X-ray treatment[163] and isolated limb perfusion also being used.[172] A double-blinded RCT of 40 patients using a topical protein–lipid complex for 3 weeks (α-lactalbumin–oleic acid) vs. saline placebo reported a 75% reduction in wart size.[173] However, this has not been investigated further.

9.0 Future directions

Warts are one of the most common skin infections and can persist for many years, but the evidence base for treatment is,

Table 2 Recommendations in particular clinical situations

Plantar warts	Cure rates are lower at this site probably due to a thicker cornified layer and subsequent poorer penetration of treatments to the lower epidermis. Paring, if used to remove excess skin from warts before treatment, should avoid damaging surrounding skin because of the risk of spreading infection
	Salicylic acid (15–40%) topical paints or ointments[12]
	Cryotherapy, fortnightly for 3–4 months[12,32]
	Salicylic acid and/or cryotherapy used with more aggressive regimens is probably more effective than standard regimens, but care is needed with worse side-effects. Combination treatments can be undertaken[10,17,20,21]
	Other treatments: dithranol,[87] 5-FU,[93] formaldehyde,[78] glutaraldehyde,[35] hyperthermia,[55] laser,[58,65] PDT,[68,73] podophyllotoxin,[90] topical immunotherapy[133,136]
Plane warts	On the backs of the hands or face, plane warts are mainly a cosmetic problem and spontaneous clearance can often be awaited. Destructive and caustic agents are more likely to produce scarring at these sites and should be used with care
	Salicylic acid cream/ointment 2–10% or cautious use of salicylic acid paint, 12–17%, used without occlusion
	Cryotherapy, milder freeze
	Topical retinoid[110,111]
	Others treatments: acupuncture,[171] cantharidin,[41] 5-FU cream,[94] formaldehyde gel, glutaraldehyde solution 10%, glycolic acid 15%,[42,43] imiquimod,[131,132] PDT,[76,115] topical immunotherapy,[138] zinc oxide,[155] zinc sulfate 10% solution[154]
Facial warts	Plane warts as above
	Treatment of filiform warts in the beard area should avoid damaging adjacent skin, which, like shaving, can spread the infection
	Cryotherapy, curettage or hyfrecation can be used
	Other treatments: glycolic acid 15%,[42,43] imiquimod,[131] laser,[174] PDT,[175,176] topical immunotherapy[177,178]
Warts in children (hand and foot warts)	Warts in children are often relatively short lived and are likely to clear within a year or two. Painful treatments are often not tolerated and should be avoided in young children if possible
	Salicylic acid (15–40%) topical paints or ointments[12]
	Cryotherapy, gentle, fortnightly for 3–4 months[12,32]
	Other treatments: cidofovir,[121] formaldehyde solution or gel,[78] glutaraldehyde 10% solution,[79] laser,[61,66] silver nitrate,[39] systemic retinoids,[114] topical immunotherapy[136]
Warts in the immunosuppressed	Treatment may not be likely to result in cure, but can help to reduce both size of warts and functional and cosmetic problems
	Standard treatments with paring, abrasive agents, salicylic acid and destructive methods (but avoiding damage to surrounding skin) can help to reduce wart bulk
	Other treatments: cidofovir systemic,[116–119] cidofovir topical,[122] contact immunotherapy,[135] imiquimod,[129,179] laser (pulsed-dye laser),[180] laser + intralesional bleomycin,[63] surgery, topical retinoid,[111] systemic retinoid[181]

FU, fluorouracil; PDT, photodynamic therapy.

for the most part, weak. Evaluating the results of studies of the large number of available treatments for warts has often been hampered by flaws in study design. In the future, the evidence for management of warts would be helped by studies in which (i) children and adults are separated into distinct treatment groups; (ii) the duration of warts before the study commences is recorded; (iii) study groups are of an adequate size; (iv) treatment runs for up to 6 months; (v) left- vs. right-side studies are avoided; (vi) treatment success is measured as clearance of all treated warts; and (vii) recurrence at 3 and 6 months following completion of treatment is included whenever possible.

For relatively easily available, inexpensive and well-tolerated treatments, a number of questions need resolution.

9.1 Salicylic acid

1 Does the concentration of SA and the treatment regimen used affect outcome?
2 Does combination with occlusion improve response rate?
3 For plantar warts, does a slightly stronger preparation (20–30% SA) used after adequate paring for up to 6 months result in wart clearance?

9.2 Caustics

1 Does treatment with phenol, silver nitrate, cantharidin or trichloroacetic acid cause warts to clear?

9.3 Cryotherapy

1 Because of the nature of the treatment, it is difficult to use a 'matched' placebo control for cryotherapy, but cryotherapy could be compared directly with another physical treatment (e.g. laser or heat treatment), and also a well-established treatment such as SA.
2 Does combination of cryotherapy with a topical agent improve clearance rates?

9.4 Virucidals

1 Controlled trials of formaldehyde and glutaraldehyde are much needed.

9.5 Antiproliferative treatments

1 Podophyllotoxin is effective in genital warts and it is less irritating than podophyllin. What treatment regimen could be tolerated on the skin and what is the response of warts?
2 Do calcipotriol or calcitriol ointments induce wart clearance?
3 What regimen or combination of treatment strengths of SA with 5-FU is most effective?

9.6 Immunotherapy

1 In a placebo-controlled study, do plane warts clear with imiquimod?
2 How effective is topical immunotherapy with DPC in wart treatment?

9.7 Pretreatment regimens

Treatments requiring an effect on the lower epidermis should employ a standardized method to remove stratum corneum before application of the test treatment. A week of daily application of SA (15–17%) under occlusion followed by daily paring or rubbing down is suggested. This regimen could be used before PDT, laser, cryotherapy etc.

10.0 Summary

Section 8 provides details of the evidence for the various treatments. Table 1 provides a summary of recommended treatments for hand warts. All treatments should be used after paring or rubbing down (debridement) of warts wherever possible. The specificity of treatment regimens has rarely been tested. The treatments should be used as advised by the manufacturers or under direction by appropriate qualified personnel who are aware of contraindications and side-effects. The suggestions in Table 1 are based on available trial evidence, case series or case reports or the authors' experience.

Table 2 lists recommendations in particular clinical situations. Many clinical trials do not specifically test treatments for different types of warts or warts in specific clinical situations. The recommendations in Table 2 are based on available trial evidence, case series or case reports or the authors' experience.

11.0 Recommended audit points

1 In the last 20 consecutive patients receiving cryotherapy treatment, were the following items recorded: (i) dose, (ii) duration, (iii) number of cycles, (iv) documentation of verbal consent?
2 In the last 20 consecutive patients receiving cryotherapy treatment, was a patient information leaflet on cryotherapy provided?

The audit recommendation of 20 cases per department is to reduce variation in the results due to a single patient, and to allow benchmarking between different units. However, departments unable to achieve this recommendation may choose to audit all cases seen in the preceding 12 months.

Acknowledgments

We are very grateful to Miss Sara Haveron (BAD Scientific Administrator) and Miss Lesley Exton (BAD Information Scientist), as well as everyone who commented on the draft during the consultation period.

References

1 Bell HK, Ormerod AD. Writing a British Association of Dermatologists clinical guideline: an update on the process and guidance for authors. *Br J Dermatol* 2009; **160**:725–8.

2 Brouwers MC, Kho ME, Browman GP *et al.* AGREE II: advancing guideline development, reporting and evaluation in health care. *CMAJ* 2010; **182**:E839–42.
3 Jarrett W. The natural history of bovine papillomavirus infection. *Adv Viral Oncol* 1986; **5**:83–102.
4 Kyriakis K, Pagana G, Michailides C *et al.* Lifetime prevalence fluctuations of common and plane viral warts. *J Eur Acad Dermatol Venereol* 2007; **21**:260–2.
5 Kilkenny M, Merlin K, Young R, Marks R. The prevalence of common skin conditions in Australian school students: 1. Common, plane and plantar viral warts. *Br J Dermatol* 1998; **138**:840–5.
6 van Haalen FM, Bruggink SC, Gussekloo J *et al.* Warts in primary schoolchildren: prevalence and relation with environmental factors. *Br J Dermatol* 2009; **161**:148–52.
7 Bruggink SC, Eekhof JA, Egberts PF *et al.* Natural course of cutaneous warts among primary schoolchildren: a prospective cohort study. *Ann Fam Med* 2013; **11**:437–41.
8 Veien NK, Madsen SM, Avrach W *et al.* The treatment of plantar warts with a keratolytic agent and occlusion. *J Dermatolog Treat* 1991; **2**:59–61.
9 Thomas KS, Keogh-Brown MR, Chalmers JR *et al.* Effectiveness and cost-effectiveness of salicylic acid and cryotherapy for cutaneous warts. An economic decision model. *Health Technol Assess* 2006; **10**:iii, ix–87.
10 Kwok CS, Holland R, Gibbs S. Efficacy of topical treatments for cutaneous warts: a meta-analysis and pooled analysis of randomized controlled trials. *Br J Dermatol* 2011; **165**:233–46.
11 Bruggink SC, Gussekloo J, Berger MY *et al.* Cryotherapy with liquid nitrogen versus topical salicylic acid application for cutaneous warts in primary care: randomized controlled trial. *CMAJ* 2010; **182**:1624–30.
12 Cockayne S, Hewitt C, Hicks K *et al.* Cryotherapy versus salicylic acid for the treatment of plantar warts (verrucae): a randomised controlled trial. *BMJ* 2011; **342**:d3271.
13 Kwok CS, Gibbs S, Bennett C *et al.* Topical treatments for cutaneous warts. *Cochrane Database Syst Rev* 2012; **9**:CD001781.
14 Tavakkolizadeh A, Povlsen B. A serious complication of topical wart treatment on the hand. *J R Soc Med* 2004; **97**:180.
15 Tiong WH, Kelly EJ. Salicylic acid burn induced by wart remover: a report of two cases. *Burns* 2009; **35**:139–40.
16 Lachapelle JM, Leroy B. Allergic contact dermatitis to colophony included in the formulation of flexible collodion BP, the vehicle of a salicylic and lactic acid wart paint. *Dermatol Clin* 1990; **8**:143–6.
17 van Brederode RL, Engel ED. Combined cryotherapy/70% salicylic acid treatment for plantar verrucae. *J Foot Ankle Surg* 2001; **40**:36–41.
18 Akarsu S, Ilknur T, Demirtaşoglu M, Ozkan S. *Verruca vulgaris*: pulsed dye laser therapy compared with salicylic acid + pulsed dye laser therapy. *J Eur Acad Dermatol Venereol* 2006; **20**:936–40.
19 Armour K, Orchard D. Treatment of palmoplantar warts with a diphencyprone and salicylic acid ointment. *Australas J Dermatol* 2006; **47**:182–5.
20 Young S, Cohen GE. Treatment of verruca plantaris with a combination of topical fluorouracil and salicylic acid. *J Am Podiatr Med Assoc* 2005; **95**:366–9.
21 Becerro de Bengoa Vallejo R, Iglesias MEL, Gómez-Martín B *et al.* Application of cantharidin and podophyllotoxin for the treatment of plantar warts. *J Am Podiatr Med Assoc* 2008; **98**:445–50.
22 Gaspar ZS, Dawber RP. An organic refrigerant for cryosurgery: fact or fiction? *Australas J Dermatol* 1997; **38**:71–2.
23 Burkhart CG, Pchalek I, Adler M, Burkhart CN. An *in vitro* study comparing temperatures of over-the-counter wart preparations with liquid nitrogen. *J Am Acad Dermatol* 2007; **57**:1019–20.
24 Caballero Martínez F, Plaza Nohales C, Pérez Canal C *et al.* [Cutaneous cryosurgery in family medicine: dimethyl ether–propane spray versus liquid nitrogen]. *Aten Primaria* 1996; **18**:211–16 (in Spanish).
25 Berth-Jones J, Hutchinson PE. Modern treatment of warts: cure rates at 3 and 6 months. *Br J Dermatol* 1992; **127**:262–5.
26 Ahmed I, Agarwal S, Ilchyshyn A *et al.* Liquid nitrogen cryotherapy of common warts: cryo-spray vs. cotton wool bud. *Br J Dermatol* 2001; **144**:1006–9.
27 Bleiker TO, Bourke JF, Lear J *et al.* A comparison of cryogun versus cotton buds for the treatment of warts. *Br J Dermatol* 1997; **137** (Suppl. s50):26.
28 Kuwahara RT, Craig SR, Amonette RA. Forceps and cotton applicator method of freezing benign lesions. *Dermatol Surg* 2001; **27**:183–4.
29 Goodheart HP. Surgical Pearl: a rapid technique for destroying small skin tags and filiform warts. *Dermatol Online J* 2003; **9**:34.
30 Sonnex TS, Camp RDR. The treatment of recalcitrant viral warts with high dose cryosurgery under local anaesthesia. *Br J Dermatol* 1988; **119** (Suppl. s33):38–9.
31 Hansen JG, Schmidt H. [Plantar warts. Occurrence and cryosurgical treatment]. *Ugeskr Laeger* 1986; **148**:173–4. (in Danish).
32 Berth-Jones J, Bourke J, Eglitis H *et al.* Value of a second freeze–thaw cycle in cryotherapy of common warts. *Br J Dermatol* 1994; **131**:883–6.
33 Connolly M, Bazmi K, O'Connell M *et al.* Cryotherapy of viral warts: a sustained 10-s freeze is more effective than the traditional method. *Br J Dermatol* 2001; **145**:554–7.
34 Bourke JF, Berth-Jones J, Hutchinson PE. Cryotherapy of common viral warts at intervals of 1, 2 and 3 weeks. *Br J Dermatol* 1995; **132**:433–6.
35 Bunney MH, Nolan MW, Williams DA. An assessment of methods of treating viral warts by comparative treatment trials based on a standard design. *Br J Dermatol* 1976; **94**:667–79.
36 Larsen PØ, Laurberg G. Cryotherapy of viral warts. *J Dermatolog Treat* 1996; **7**:29–31.
37 Youn SH, Kwon IH, Park EJ *et al.* A two-week interval is better than a three-week interval for reducing the recurrence rate of hand-foot viral warts after cryotherapy: a tretrospective review of 560 hand-foot viral wart patients. *Ann Dermatol* 2011; **23**:53–60.
38 Ebrahimi S, Dabiri N, Jamshidnejad E, Sarkari B. Efficacy of 10% silver nitrate solution in the treatment of common warts: a placebo-controlled, randomized, clinical trial. *Int J Dermatol* 2007; **46**:215–17.
39 Yazar S, Başaran E. Efficacy of silver nitrate pencils in the treatment of common warts. *J Dermatol* 1994; **21**:329–33.
40 Banihashemi M, Pezeshkpoor F, Yazdanpanah MJ, Family S. Efficacy of 80% phenol solution in comparison with cryotherapy in the treatment of common warts of hands. *Singapore Med J* 2008; **49**:1035–7.
41 Kartal Durmazlar SP, Atacan D, Eskioglu F. Cantharidin treatment for recalcitrant facial flat warts: a preliminary study. *J Dermatolog Treat* 2009; **20**:114–19.
42 Borbujo J, Olmos O, Zamora E *et al.* Treatment of verrucae plana with 15% glycolic acid. *Int J Dermatol* 2000; **39**:236–7.
43 Rodríguez-Cerdeira C, Sánchez-Blanco E. Glycolic acid 15% plus salicylic acid 2%: a new therapeutic pearl for facial flat warts. *J Clin Aesthet Dermatol* 2011; **4**:62–4.

44 Halasz CL. Treatment of warts with topical pyruvic acid: with and without added 5-fluorouracil. *Cutis* 1998; **62**:283–5.

45 Donaldson MR, Stetson CL. Hypertrophic scarring after treatment with fluorouracil, 2%, in pyruvic acid, 98%, for *Verruca vulgaris*. *Arch Dermatol* 2010; **146**:213–14.

46 Vali A, Ferdowsi F. Evaluation of the efficacy of 50% citric acid solution in plane wart treatment. *Indian J Dermatol* 2007; **52**:96–8.

47 Bhat RM, Vidya K, Kamath G. Topical formic acid puncture technique for the treatment of common warts. *Int J Dermatol* 2001; **40**:415–19.

48 Shamsadini S, Baghery MH. Treatment of warts with topical formic acid. *Iran J Med Sci* 2005; **30**:199.

49 Faghihi G, Vali A, Radan M *et al.* A double-blind, randomized trial of local formic acid puncture technique in the treatment of common warts. *Skinmed* 2010; **8**:70–1.

50 Godley MJ, Bradbeer CS, Gellan M, Thin RN. Cryotherapy compared with trichloroacetic acid in treating genital warts. *Genitourin Med* 1987; **63**:390–2.

51 Pezeshkpoor F, Banihashemi M, Yazdanpanah MJ *et al.* Comparative study of topical 80% trichloroacetic acid with 35% trichloroacetic acid in the treatment of the common wart. *J Drugs Dermatol* 2012; **11**:e66–9.

52 Jennings MB, Ricketti J, Guadara J *et al.* Treatment for simple plantar verrucae: monochloroacetic acid and 10% formaldehyde versus 10% formaldehyde alone. *J Am Podiatr Med Assoc* 2006; **96**:53–8.

53 Baser NT, Yalaz B, Yilmaz AC *et al.* An unusual and serious complication of topical wart treatment with monochloroacetic acid. *Int J Dermatol* 2008; **47**:1295–7.

54 Stern P, Levine N. Controlled localized heat therapy in cutaneous warts. *Arch Dermatol* 1992; **128**:945–8.

55 Huo W, Gao X-H, Sun X-P *et al.* Local hyperthermia at 44 °C for the treatment of plantar warts: a randomized, patient-blinded, placebo-controlled trial. *J Infect Dis* 2010; **201**:1169–72.

56 Gao XH, Gao D, Sun XP *et al.* Non-ablative controlled local hyperthermia for common warts. *Chin Med J* 2009; **122**:2061–3.

57 Lelliott PE, Robinson C. A retrospective study to evaluate verrucae regrowth following electrosurgery. *Br J Pod* 1999; **2**:84–8.

58 Robson KJ, Cunningham NM, Kruzan KL *et al.* Pulsed-dye laser versus conventional therapy in the treatment of warts: a prospective randomized trial. *J Am Acad Dermatol* 2000; **43**:275–80.

59 Park HS, Choi WS. Pulsed dye laser treatment for viral warts: a study of 120 patients. *J Dermatol* 2008; **35**:491–8.

60 Ross BS, Levine VJ, Nehal K *et al.* Pulsed dye laser treatment of warts: an update. *Dermatol Surg* 1999; **25**:377–80.

61 Sethuraman G, Richards KA, Hiremagalore RN, Wagner A. Effectiveness of pulsed dye laser in the treatment of recalcitrant warts in children. *Dermatol Surg* 2010; **36**:58–65.

62 Kauvar AN, Geronemus RG. Pulsed-dye laser versus conventional therapy in the treatment of warts. *J Am Acad Dermatol* 2001; **45**:151–2.

63 Pollock B, Sheehan-Dare R. Pulsed dye laser and intralesional bleomycin for treatment of resistant viol hand warts. *Lasers Surg Med* 2002; **30**:135–40.

64 Dobson JS, Harland CC. Pulsed dye laser and intralesional bleomycin for the treatment of recalcitrant cutaneous warts. *Lasers Surg Med* 2014; **46**:112–16.

65 Kopera D. Verrucae vulgares: flashlamp-pumped pulsed dye laser treatment in 134 patients. *Int J Dermatol* 2003; **42**:905–8.

66 Park HS, Kim JW, Jang SJ, Choi JC. Pulsed dye laser therapy for pediatric warts. *Pediatr Dermatol* 2007; **24**:177–81.

67 Han TY, Lee JH, Lee CK *et al.* Long-pulsed Nd:YAG laser treatment of warts: report on a series of 369 cases. *J Korean Med Sci* 2009; **24**:889–93.

68 Stender IM, Na R, Fogh H *et al.* Photodynamic therapy with 5-aminolaevulinic acid or placebo for recalcitrant foot and hand warts: randomised double-blind trial. *Lancet* 2000; **355**:963–6.

69 Fabbrocini G, Di Costanzo MP, Riccardo AM *et al.* Photodynamic therapy with topical delta-aminolaevulinic acid for the treatment of plantar warts. *J Photochem Photobiol, B* 2001; **61**:30–4.

70 Schroeter CA, Kaas L, Waterval JJ *et al.* Successful treatment of periungual warts using photodynamic therapy: a pilot study. *J Eur Acad Dermatol Venereol* 2007; **21**:1170–4.

71 Stender IM, Wulf HC. Photodynamic therapy of recalcitrant warts with 5-aminolevulinic acid: a retrospective analysis. *Acta Derm Venereol* 1999; **79**:400–1.

72 Wang YS, Tay YK, Kwok C *et al.* Photodynamic therapy with 20% aminolevulinic acid for the treatment of recalcitrant viral warts in an Asian population. *Int J Dermatol* 2007; **46**:1180–4.

73 Yoo KH, Kim BJ, Kim MN. Enhanced efficacy of photodynamic therapy with methyl 5-aminolevulinic acid in recalcitrant periungual warts after ablative carbon dioxide fractional laser: a pilot study. *Dermatol Surg* 2009; **35**:1927–32.

74 Fernandez-Guarino M, Harto A, Jaen P. Treatment of recalcitrant viral warts with pulsed dye laser MAL-PDT. *J Dermatolog Treat* 2011; **22**:226–8.

75 Ziolkowski P, Osiecka BJ, Siewinski M *et al.* Pretreatment of plantar warts with azone enhances the effect of 5-aminolevulinic acid photodynamic therapy. *J Environ Pathol Toxicol Oncol* 2006; **25**:403–9.

76 Lu YG, Wu JJ, He Y *et al.* Efficacy of topical aminolevulinic acid photodynamic therapy for the treatment of verruca planae. *Photomed Laser Surg* 2010; **28**:561–3.

77 Li Q, Jiao B, Zhou F *et al.* Comparative study of photodynamic therapy with 5%, 10% and 20% aminolevulinic acid in the treatment of generalized recalcitrant facial verruca plana: a randomized clinical trial. *J Eur Acad Dermatol Venereol* 2013. doi:10.1111/jdv.12319 [Epub ahead of print].

78 Vickers CF. Treatment of plantar warts in children. *BMJ* 1961; **2**:743–5.

79 Hirose R, Hori M, Shukuwa T *et al.* Topical treatment of resistant warts with glutaraldehyde. *J Dermatol* 1994; **21**:248–53.

80 Fujisawa Y, Furuta J, Kawachi Y, Otsuka F. Deep plantaris ulceration secondary to the topical treatment of wart with glutaraldehyde. *J Dermatol* 2009; **36**:618–19.

81 Egawa K, Ono T. Topical vitamin D3 derivatives for recalcitrant warts in three immunocompromised patients. *Br J Dermatol* 2004; **150**:374–6.

82 Inaba H, Suzuki T, Adachi A, Tomita Y. Successful treatment of warts with a combination of maxacalcitol ointment and salicylic acid sticking plaster. *J Dermatol* 2006; **33**:383–5.

83 Imagawa I, Suzuki H. Successful treatment of refractory warts with topical vitamin D3 derivative (maxacalcitol, 1α,25-dihydroxy-22-oxacalcitriol) in 17 patients. *J Dermatol* 2007; **34**:264–6.

84 Labandeira J, Vazquez-Blanco M, Paredes C *et al.* Efficacy of topical calcipotriol in the treatment of a giant viral wart. *Pediatr Dermatol* 2005; **22**:375–6.

85 Hayashi J, Matsui C, Mitsuishi T *et al.* Treatment of localized epidermodysplasia verruciformis with tacalcitol ointment. *Int J Dermatol* 2002; **41**:817–20.

86 Flindt-Hansen H, Tikjøb G, Brandrup F. Wart treatment with anthralin. *Acta Derm Venereol* 1984; **64**:177–9.

87 Hjorth N, Madsen K, Norgaard M. Anthralin stick (Anthraderm) in the treatment of mosaic warts. *Acta Derm Venereol* 1986; **66**:181–2.

88 Mirceva V, Jessberger B, Konstantinow A *et al.* Treatment of common warts with dithranol salicylic acid-containing ointment – non-interventional trial. *Aktuelle Dermatol* 2008; **34**:428–32.

89 Mirceva V, Jessberger B, Papadopulos NA *et al.* Treatment of cutaneous warts with a wart cream containing anthralin and salicylic acid: an efficacy study on 44 patients. *Aktuelle Dermatol* 2007; **33**:422–7.

90 Duthie DA, McCallum DI. Treatment of plantar warts with elastoplast and podophyllin. *BMJ* 1951; **2**:216–18.

91 Kaçar N, Taşlı L, Korkmaz S *et al.* Cantharidin-podophylotoxin-salicylic acid versus cryotherapy in the treatment of plantar warts: a randomized prospective study. *J Eur Acad Dermatol Venereol* 2012; **26**:889–93.

92 Hursthouse MW. A controlled trial on the use of topical 5-fluorouracil on viral warts. *Br J Dermatol* 1975; **92**:93–6.

93 Salk RS, Grogan KA, Chang TJ. Topical 5% 5-fluorouracil cream in the treatment of plantar warts: a prospective, randomized, and controlled clinical study. *J Drugs Dermatol* 2006; **5**:418–24.

94 Lee S, Kim JG, Chun SI. Treatment of verruca plana with 5% 5-fluorouracil ointment. *Dermatologica* 1980; **160**:383–9.

95 Luk NM, Tang WY, Tang NL *et al.* Topical 5-fluorouracil has no additional benefit in treating common warts with cryotherapy: a single-centre, double-blind, randomized, placebo-controlled trial. *Clin Exp Dermatol* 2006; **31**:394–7.

96 Zschocke I, Hartmann A, Schlöbe A *et al.* [Efficacy and benefit of a 5-FU/salicylic acid preparation in the therapy of common and plantar warts – systematic literature review and meta-analysis]. *J Dtsch Dermatol Ges* 2004; **2**:187–93 (in German).

97 Yazdanfar A, Farshchian M, Fereydoonnejad M. Treatment of common warts with an intralesional mixture of 5-fluorouracil, lidocaine, and epinephrine: a prospective placebo-controlled, double-blind randomized trial. *Dermatol Surg* 2008; **34**:656–9.

98 Işçimen A, Aydemir EH, Göksügür N, Engin B. Intralesional 5-fluorouracil, lidocaine and epinephrine mixture for the treatment of verrucae: a prospective placebo-controlled, single-blind randomized study. *J Eur Acad Dermatol Venereol* 2004; **18**:455–8.

99 Lewis TG, Nydorf ED. Intralesional bleomycin for warts: a review. *J Drugs Dermatol* 2006; **5**:499–504.

100 Hayes ME, O'Keefe EJ. Reduced dose of bleomycin in the treatment of recalcitrant warts. *J Am Acad Dermatol* 1986; **15**:1002–6.

101 AlGhamdi KM, Khurram H. Successful treatment of periungual warts with diluted bleomycin using translesional multipuncture technique: a pilot prospective study. *Dermatol Surg* 2011; **37**:486–92.

102 Munn SE, Higgins E, Marshall M, Clement M. A new method of intralesional bleomycin therapy in the treatment of recalcitrant warts. *Br J Dermatol* 1996; **135**:969–71.

103 van der Velden EM, Ijsselmuiden OE, Drost BH, Baruchin AM. Dermatography with bleomycin as a new treatment for *Verrucae vulgaris*. *Int J Dermatol* 1997; **36**:145–50.

104 Soni P, Khandelwal K, Aara N *et al.* Efficacy of intralesional bleomycin in palmo-plantar and periungual warts. *J Cutan Aesthet Surg* 2011; **4**:188–91.

105 Bunney MH, Nolan MW, Buxton PK *et al.* The treatment of resistant warts with intralesional bleomycin: a controlled clinical trial. *Br J Dermatol* 1984; **111**:197–207.

106 Adalatkhah H, Khalilollahi H, Amini N, Sadeghi-Bazargani H. Compared therapeutic efficacy between intralesional bleomycin and cryotherapy for common warts: a randomized clinical trial. *Dermatol Online J* 2007; **13**:4.

107 Dhar SB, Rashid MM, Islam A, Bhuiyan M. Intralesional bleomycin in the treatment of cutaneous warts: a randomized clinical trial comparing it with cryotherapy. *Indian J Dermatol Venereol Leprol* 2009; **75**:262–7.

108 Abess A, Keel DM, Graham BS. Flagellate hyperpigmentation following intralesional bleomycin treatment of verruca plantaris. *Arch Dermatol* 2003; **139**:337–9.

109 Yamamoto T. Bleomycin and the skin. *Br J Dermatol* 2006; **155**:869–75.

110 Kubeyinje EP. Evaluation of the efficacy and safety of 0.05% tretinoin cream in the treatment of plane warts in Arab children. *J Dermatolog Treat* 1996; **7**:21–2.

111 Euvrard S, Verschoore M, Touraine JL *et al.* Topical retinoids for warts and keratoses in transplant recipients. *Lancet* 1992; **340**:48–9.

112 Gupta R. Plantar warts treated with topical adapalene. *Indian J Dermatol* 2011; **56**:513–14.

113 Choi YL, Lee KJ, Kim WS *et al.* Treatment of extensive and recalcitrant viral warts with acitretin. *Int J Dermatol* 2006; **45**:480–2.

114 Gelmetti C, Cerri D, Schiuma AA *et al.* Treatment of extensive warts with etretinate: a clinical trial in 20 children. *Pediatr Dermatol* 1987; **4**:254–8.

115 Al-Hamamy HR, Salman HA, Abdulsattar NA. Treatment of plane warts with a low-dose oral isotretinoin. *ISRN Dermatol* 2012; **2012**:163929.

116 Cusack C, Fitzgerald D, Clayton TM, Irvine AD. Successful treatment of florid cutaneous warts with intravenous cidofovir in an 11-year-old girl. *Pediatr Dermatol* 2008; **25**:387–9.

117 Grone D, Treudler R, de Villiers EM *et al.* Intravenous cidofovir treatment for recalcitrant warts in the setting of a patient with myelodysplastic syndrome. *J Eur Acad Dermatol Venereol* 2006; **20**:202–5.

118 Hivnor C, Shepard JW, Shapiro MS, Vittorio CC. Intravenous cidofovir for recalcitrant *Verruca vulgaris* in the setting of HIV. *Arch Dermatol* 2004; **140**:13–14.

119 Kottke MD, Parker SR. Intravenous cidofovir-induced resolution of disfiguring cutaneous human papillomavirus infection. *J Am Acad Dermatol* 2006; **55**:533–6.

120 Mackintosh L, Parker A, Leman J. Intravenous cidofovir for the treatment of florid cutaneous warts in association with chronic graft-versus-host disease. *Br J Dermatol* 2012; **167** (Suppl. 1):116.

121 Field S, Irvine AD, Kirby B. The treatment of viral warts with topical cidofovir 1%: our experience of seven paediatric patients. *Br J Dermatol* 2009; **160**:223–4.

122 Tobin AM, Cotter M, Irvine AD, Kirby B. Successful treatment of a refractory verruca in a child with acute lymphoblastic leukaemia with topical cidofovir. *Br J Dermatol* 2005; **152**:386–8.

123 Broganelli P, Chiaretta A, Fragnelli B, Bernengo MG. Intralesional cidofovir for the treatment of multiple and recalcitrant cutaneous viral warts. *Dermatol Ther* 2012; **25**:468–71.

124 Bienvenu B, Martinez F, Devergie A *et al.* Topical use of cidofovir induced acute renal failure. *Transplantation* 2002; **73**:661–2.

125 Focht DR, Spicer C, Fairchok MP. The efficacy of duct tape versus cryotherapy in the treatment of *Verruca vulgaris* (the common wart). *Arch Pediatr Adolesc Med* 2002; **156**:971–4.

126 de Haen M, Spigt MG, van Uden CJ *et al.* Efficacy of duct tape versus placebo in the treatment of *Verruca vulgaris* (warts) in primary school children. *Arch Pediatr Adolesc Med* 2006; **160**:1121–5.

127 Wenner R, Askari SK, Cham PM *et al.* Duct tape for the treatment of common warts in adults: a double-blind randomized controlled trial. *Arch Dermatol* 2007; **143**:309–13.

128 Grussendorf-Conen EI, Jacobs S, Rübben A, Dethlefsen U. Topical 5% imiquimod long-term treatment of cutaneous warts resistant to standard therapy modalities. *Dermatology* 2002; **205**:139–45.

129 Hengge UR, Goos M, Arndt R. Topical treatment of warts and mollusca with imiquimod. *Ann Intern Med* 2000; **132**:95.

130 Kim SY, Jung SK, Lee SG *et al.* New alternative combination therapy for recalcitrant common warts: the efficacy of imiquimod

5% cream and duct tape combination therapy. *Ann Dermatol* 2013; **25**:261–3.
131 Kim MB, Ko HC, Jang HS *et al.* Treatment of flat warts with 5% imiquimod cream. *J Eur Acad Dermatol Venereol* 2006; **20**:1349–50.
132 Oster-Schmidt C. Imiquimod: a new possibility for treatment-resistant verrucae planae. *Arch Dermatol* 2001; **137**:666–7.
133 Buckley DA, Keane FM, Munn SE *et al.* Recalcitrant viral warts treated by diphencyprone immunotherapy. *Br J Dermatol* 1999; **141**:292–6.
134 Upitis JA, Krol A. The use of diphenylcyclopropenone in the treatment of recalcitrant warts. *J Cutan Med Surg* 2002; **6**:214–17.
135 Audrain H, Siddiqui H, Buckley DA. Diphencyprone immunotherapy for viral warts in immunosuppressed patients. *Br J Dermatol* 2013; **168**:1138–9.
136 Micali G, Nasca MR, Tedeschi A *et al.* Use of squaric acid dibutylester (SADBE) for cutaneous warts in children. *Pediatr Dermatol* 2000; **17**:315–18.
137 Silverberg JI, Silverberg NB. Adjunctive trichloroacetic acid therapy enhances squaric acid response to *Verruca vulgaris*. *J Drugs Dermatol* 2012; **11**:1228–30.
138 Salem A, Nofal A, Hosny D. Treatment of common and plane warts in children with topical viable Bacillus Calmette–Guérin. *Pediatr Dermatol* 2013; **30**:60–3.
139 Horn TD, Johnson SM, Helm RM, Roberson PK. Intralesional immunotherapy of warts with mumps, *Candida*, and *Trichophyton* skin test antigens: a single-blinded, randomized, and controlled trial. *Arch Dermatol* 2005; **141**:589–94.
140 Phillips RC, Ruhl TS, Pfenninger JL, Garber MR. Treatment of warts with *Candida* antigen injection. *Arch Dermatol* 2000; **136**:1274–5.
141 Signore RJ. *Candida albicans* intralesional injection immunotherapy of warts. *Cutis* 2002; **70**:185–92.
142 Mitsuishi T, Iida K, Kawana S. Cimetidine treatment for viral warts enhances IL-2 and IFN-γ expression but not IL-18 expression in lesional skin. *Eur J Dermatol* 2003; **13**:445–8.
143 Gooptu C, James MP. Recalcitrant viral warts: results of treatment with the KTP laser. *Clin Exp Dermatol* 1999; **24**:60–3.
144 Rogers CJ, Gibney MD, Siegfried EC *et al.* Cimetidine therapy for recalcitrant warts in adults: is it any better than placebo? *J Am Acad Dermatol* 1999; **41**:123–7.
145 Lee SH, Rose B, Thompson CH, Cossart Y. Plantar warts of defined aetiology in adults and unresponsiveness to low dose cimetidine. *Australas J Dermatol* 2001; **42**:220–1.
146 Karaman G, Sendur N, Sevk E. Ranitidine therapy for recalcitrant warts in adults: a preliminary study. *J Eur Acad Dermatol Venereol* 2001; **15**:495–6.
147 Hamblin TJ. Long-lasting response of therapy-resistant viral warts to treatment with interleukin-2 in a patient with chronic lymphocytic leukemia (CLL) and profound immunodeficiency. *Leuk Res* 2007; **31**:413–14.
148 Lin JH, Wang KY, Kraft S, Roberts RL. Resolution of warts in association with subcutaneous immunoglobulin in immune deficiency. *Pediatr Dermatol* 2009; **26**:155–8.
149 Tandeter H, Tandeter ER. Treatment of plantar warts with oral valacyclovir. *Am J Med* 2005; **118**:689–90.
150 López-García DR, Gómez-Flores M, Arce-Mendoza AY *et al.* Oral zinc sulfate for unresponsive cutaneous viral warts: too good to be true? A double-blind, randomized, placebo-controlled trial. *Clin Exp Dermatol* 2009; **34**:e984–5.
151 Al-Gurairi FT, Al-Waiz M, Sharquie KE. Oral zinc sulphate in the treatment of recalcitrant viral warts: randomized placebo-controlled clinical trial. *Br J Dermatol* 2002; **146**:423–31.
152 Yaghoobi R, Sadighha A, Baktash D. Evaluation of oral zinc sulfate effect on recalcitrant multiple viral warts: a randomized placebo-controlled clinical trial. *J Am Acad Dermatol* 2009; **60**:706–8.
153 Sadighha A. Oral zinc sulphate in recalcitrant multiple viral warts: a pilot study. *J Eur Acad Dermatol Venereol* 2009; **23**:715–16.
154 Sharquie KE, Khorsheed AA, Al-Nuaimy AA. Topical zinc sulphate solution for treatment of viral warts. *Saudi Med J* 2007; **28**:1418–21.
155 Khattar JA, Musharrafieh UM, Tamim H, Hamadeh GN. Topical zinc oxide vs. salicylic acid-lactic acid combination in the treatment of warts. *Int J Dermatol* 2007; **46**:427–30.
156 Burns DA. 'Warts and all' – the history and folklore of warts: a review. *J R Soc Med* 1992; **85**:37–40.
157 Rankin S, Swinscoe M. Alternative treatments and folk remedies in the treatment of warts. *Br J Pod* 2002; **5**:12–14.
158 Spanos NP, Williams V, Gwynn MI. Effects of hypnotic, placebo, and salicylic acid treatments on wart regression. *Psychosom Med* 1990; **52**:109–14.
159 Surman OS, Gottlieb SK, Hackett TP, Silverberg EL. Hypnosis in the treatment of warts. *Arch Gen Psychiatry* 1973; **28**:439–41.
160 Shenefelt PD. Biofeedback, cognitive-behavioral methods, and hypnosis in dermatology: is it all in your mind? *Dermatol Ther* 2003; **16**:114–22.
161 Dave R, Monk B, Mahaffey P. Spontaneous disappearance of refractory viral warts at distant sites following carbon-dioxide laser treatment. *Br J Plast Surg* 2002; **55**:696–8.
162 Harkness EF, Abbot NC, Ernst E. A randomized trial of distant healing for skin warts. *Am J Med* 2000; **108**:448–52.
163 Meineke V, Reichrath J, Reinhold U, Tilgen W. Verrucae vulgares in children: successful simulated X-ray treatment (a suggestion-based therapy). *Dermatology* 2002; **204**:287–9.
164 Bedi MK, Shenefelt PD. Herbal therapy in dermatology. *Arch Dermatol* 2002; **138**:232–42.
165 Dehghani F, Merat A, Panjehshahin MR, Handjani F. Healing effect of garlic extract on warts and corns. *Int J Dermatol* 2005; **44**:612–15.
166 Bohlooli S, Mohebipoor A, Mohammadi S *et al.* Comparative study of fig tree efficacy in the treatment of common warts (*Verruca vulgaris*) vs. cryotherapy. *Int J Dermatol* 2007; **46**:524–6.
167 Zedan H, Hofny ER, Ismail SA. Propolis as an alternative treatment for cutaneous warts. *Int J Dermatol* 2009; **48**:1246–9.
168 Rahimi AR, Emad M, Rezaian GR. Smoke from leaves of *Populus euphratica* Olivier vs. conventional cryotherapy for the treatment of cutaneous warts: a pilot, randomized, single-blind, prospective study. *Int J Dermatol* 2008; **47**:393–7.
169 Kainz JT, Kozel G, Haidvogl M, Smolle J. Homoeopathic versus placebo therapy of children with warts on the hands: a randomized, double-blind clinical trial. *Dermatology* 1996; **193**:318–20.
170 Gengoux P. Homeopathic versus placebo therapy of children with warts on the hands. *Dermatology* 1997; **195**:183.
171 Ning S, Li F, Qian L *et al.* The successful treatment of flat warts with auricular acupuncture. *Int J Dermatol* 2012; **51**:211–15.
172 Damian DL, Barnetson RS, Rose BR *et al.* Treatment of refractory hand warts by isolated limb infusion with melphalan and actinomycin D. *Australas J Dermatol* 2001; **42**:106–9.
173 Gustafsson L, Leijonhufvud I, Aronsson A *et al.* Treatment of skin papillomas with topical α-lactalbumin–oleic acid. *N Engl J Med* 2004; **350**:2663–72.
174 Li Y, Yang K. Treatment of recalcitrant-pigmented flat warts using frequency-doubled Q-switched Nd-YAG laser. *Lasers Surg Med* 2001; **29**:244–7.
175 Caucanas M, Gillard P, Vanhooteghem O. Efficiency of photodynamic therapy in the treatment of diffuse facial viral warts in an immunosuppressed patient: towards a gold standard? *Case Rep Dermatol* 2010; **2**:207–13.

176 Durani BK, Jappe U. Successful treatment of facial plane warts with imiquimod. *Br J Dermatol* 2002; **147**:1018.
177 Aghaei S. Treatment of disseminated facial warts through contact immunotherapy with diphenylcyclopropenone (DPCP). *Dermatol Online J* 2006; **12**:10.
178 Hama N, Hatamochi A, Hayashi S *et al.* Usefulness of topical immunotherapy with squaric acid dibutylester for refractory common warts on the face and neck. *J Dermatol* 2009; **36**:660–2.
179 Weisshaar E, Gollnick H. Potentiating effect of imiquimod in the treatment of verrucae vulgares in immunocompromised patients. *Acta Derm Venereol* 2000; **80**:306–7.
180 Läuchli S, Kempf W, Dragieva G *et al.* CO_2 laser treatment of warts in immunosuppressed patients. *Dermatology* 2003; **206**:148–52.
181 Monastirli A, Matsouka P, Pasmatzi E *et al.* Complete remission of recalcitrant viral warts under oral isotretinoin in a patient with low-grade B-cell lymphoma. *Acta Derm Venereol* 2005; **85**:358–60.

Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website:

Data S1. Literature search strategies.

Appendix 1

Levels of evidence

Level of evidence[a]	Type of evidence
1++	High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
1+	Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias
1−	Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias
2++	High-quality systematic reviews of case–control or cohort studies High-quality case–control or cohort studies with a very low risk of confounding, bias or chance and a high probability that the relationship is causal
2+	Well-conducted case–control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal
2−	Case–control or cohort studies with a high risk of confounding, bias or chance and a significant risk that the relationship is not causal
3	Nonanalytical studies (for example case reports, case series)
4	Expert opinion, formal consensus

RCT, randomized controlled trial. [a]Studies with a level of evidence '−' should not be used as a basis for making a recommendation.

Appendix 2

Strength of recommendation

Class	Evidence
A	At least one meta-analysis, systematic review or RCT rated as 1++, and directly applicable to the target population, or A systematic review of RCTs or a body of evidence consisting principally of studies rated as 1+, directly applicable to the target population and demonstrating overall consistency of results Evidence drawn from a NICE technology appraisal
B	A body of evidence including studies rated as 2++, directly applicable to the target population and demonstrating overall consistency of results, or Extrapolated evidence from studies rated as 1++ or 1+
C	A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results, or Extrapolated evidence from studies rated as 2++
D	Evidence level 3 or 4, or Extrapolated evidence from studies rated as 2+, or Formal consensus
D (GPP)	A good practice point (GPP) is a recommendation for best practice based on the experience of the guideline development group

RCT, randomized controlled trial; NICE, National Institute for Health and Care Excellence.