Treatment of warts and molluscum: what does the evidence show?

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Purpose of review
Warts and molluscum contagiosum are very common viral skin infections, usually presenting in childhood. Despite the large number of people affected by them, high-quality trials of treatment are few and treatment is often chosen on the basis of cost, convenience and tradition.

Recent findings
Over recent years, two further trials of the most commonly used treatments for warts, salicylic acid and cryotherapy, have been performed and for molluscum contagiosum, there is growing evidence for the use of irritants. For both infections, there are new evaluations of immunological approaches to therapy.

Summary
Strong, high-quality evidence for treatments used very frequently for warts or molluscum is still lacking, but recent publications have helped to strengthen or weaken belief in commonly used therapies and to add weight to the immunological approach to management.

Keywords
molluscum contagiosum, treatment, warts

INTRODUCTION

Both warts and molluscum contagiosum are likely to resolve spontaneously, but as clearance can take months or years, treatment is usually sought for cosmetic reasons, pain or, particularly for warts, interference with function. Molluscum contagiosum lesions are often asymptomatic, but can become inflamed and pustular and lesions may number over a hundred.

This review will focus on treatments recently reported or reconsidered, and wherever possible, how children respond.

WARTS

Current knowledge of the numerous remedies for warts is not based on much strong evidence, even though many treatments are in regular use [1▪,2]. Where treatment trials have been placebo controlled, a 20–30% response rate is expected for placebo treatment. Spontaneous clearance in children is generally quicker than in adults: two-thirds resolve spontaneously in 2 years and 80% by 4 years [3].

Destructive treatments

Damage to the epidermis that harbors the virus can act by removing the infected keratinocytes but may also stimulate an inflammatory and possibly an immunological reaction.

SALICYLIC ACID

There is good evidence that regular, topical salicylic acid can speed wart clearance in clinical trials. Compliance rate with unsupervised home treatment, however, is often poor, with perhaps only a third persisting with regular and prolonged applications [4].

Studies of topical salicylic acid (12–50%) applied 5–7 times per week for 12 weeks suggest a clearance rate better than placebo [2]. In a meta-analysis of five trials, the cure rate was 52% with salicylic acid compared with 23% for placebo [5].

In a study that separated children under 12 years of age in the analysis, their clearance rate was 24%

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Curr Opin Pediatr 2016, 28:490–499
DOI:10.1097/MOP.0000000000000377

KEY POINTS

- Warts and molluscum contagiosum can be left untreated as spontaneous clearance is likely within 2 years.
- Salicylic acid and/or cryotherapy remain the treatments of choice for most warts.
- Irritants are the treatment of choice for young children with molluscum, with cryotherapy an option for the older child.
- For recalcitrant warts or molluscum, or for immunosuppressed patients, a large number of other treatments are available, all of which have some reported success.

for salicylic acid treatment and 16% without treatment [6]. In an adults-only trial, salicylic acid applied under an occlusive patch cleared warts in 68% of patients compared with 28% for patients treated with a placebo patch [7].

CAUSTICS

Applications that can result in more rapid and vigorous damage to the epidermis include phenol, cantharidin and the monochloroacetic, trichloroacetic, formic and pyruvic acids (Table 1) [8–29]. Application must be accurate, so as not to damage surrounding skin, and may be painful.

A recently reported randomized controlled trial of saturated monochloroacetic acid compared with cryotherapy in just over 200 participants involved both children and adults but with a mean age in the pediatric range [30]. Rates of clearance of all warts were comparable for both treatments, but higher in children compared with adults and higher in plantar warts compared with hand warts.

Pyruvic acid has also been trialled recently and seems to be comparable in effect to salicylic acid [31]. It is a keratolytic, and like salicylic acid, causes softening and sloughing of the upper layers of the epidermis. It is used as a chemical peel at 50% for short application, but in trials for warts, 70% pyruvic acid in 70% ethanol has been used, and as with salicylic acid, care must be taken to avoid erosion of normal skin.

Bleomycin causes necrosis and has shown both encouraging and also disappointing results (Table 1).

OCCLUSOTHERAPY

Occlusion included in trials of topical therapy has been suggested to enhance the effect of the topical treatment [7,32], but occlusotherapy as a standalone treatment gives no significant benefit over placebo [33,34].

Cryotherapy is a very common treatment in dermatology practice but is a painful treatment and therefore one often not well received by children. Placebo-controlled trials for cryotherapy are of course difficult, but there are a number of studies comparing freezing with another treatment. Reported rates of clearance range from 0 to 69% with a mean of 49% [5], with aggressive freezing more effective than gentle application, and hand warts clearing better than plantar warts.

Recently, two trials comparing cryotherapy with salicylic acid have given useful data. One study compared gentle cryotherapy with 50% salicylic acid ointment for plantar warts in individuals over 12 years of age and found only 14% cure rate for either treatment by 12 weeks [35]. A second comparative trial of 250 participants included a no-treatment arm, and used a more aggressive cryotherapy protocol and 40% salicylic acid ointment. By 13 weeks, cure was obtained in 8% (no treatment), 15% (salicylic acid) and 49% (cryotherapy) [6]. In children below 12 years, the cure rates were 29, 42 and 52%, respectively. With this information, it is reasonable to conclude that, when used under regular supervision in a trial, cryotherapy is as effective as salicylic acid.

There is some evidence from retrospective analyses that the combination of salicylic acid and cryotherapy is better than either alone [5,36].

LASER

The pulsed dye laser is the most commonly used laser for treating warts and many operators will treat children, using topical or sometimes injected anesthesia. On the basis of prospective or retrospective reports, the clearance rate has been found to be approximately 50%. It can be a useful modality for recalcitrant warts and treatment of warts in more challenging situations, such as the immunosuppressed and periungual warts.

In a recent retrospective analysis, 66 children were among the 227 patients with recalcitrant warts treated with pulsed dye laser. In the 208 who were followed up, 86% were regarded as having treatment success, which included complete clearance and almost clear. On average, patients received six treatments [37].

Photodynamic therapy (PDT) using aminolaevulinic acid as a cream application in combination with visible light can be a painful procedure and even with topical analgesia, may not be tolerable for children. Usually, the treatment is given 2 or

Table 1. Wart treatments not discussed in detail in the text

Treatment	Comparator	Number	Details of treatment	Clearance rate (comparator)	References
Phenol	Cryotherapy	$n=30$ phenol, 30 cryotherapy Children >7 years included	80% phenol, applied weekly for 6 weeks. Cryotherapy weekly. 7/30 withdrew due to pain	82% of warts (70% freezing) at 6 weeks	[8]
Cantharidin	Nil	$N=15$	0.7% cantharidin, every 3 weeks up to 16 weeks. Facial plane warts	100% at 16 weeks	[9]
Formic acid	Water	$n=50$ formic acid, 50 placebo	85% formic acid applied to surface and pricked into warts. Repeated on alternate days to a maximum of 12 treatments	92% patients (6% placebo) at 3 months	[10]
Bleomycin	Cryotherapy	$N=40$ bleomycin, 40 cryotherapy	Bleomycin 1 μ/ml injected into warts, 3-weekly up to 4 treatments	97% warts (82% cryotherapy) at 8 weeks	[11]
	Saline	$N=22$ warts, 27 warts placebo	1% bleomycin in saline injected into wart, repeated fortnightly up to 3 treatments	18% warts (42% placebo)	[12]
	Nil	$N=1$, aged 14	1 μ/ml bleomycin, pricked into wart. Repeated monthly for 5 months	Cleared	[13]
PDT	Nil	$N=20$ Children included	20% ALA cream + visible light, fortnightly up to 13 treatments. Pretreatment paring. Periungual warts	90% warts clear at mean of 5 months	[14]
	Placebo cream	$N=45$ Adults	20% ALA cream + visible light, weekly, up to three treatments. Pretreatment paring	56% warts (42% placebo) at week 18	[15]
	Placebo cream	$N=67$ Adults	20% ALA cream + visible light, weekly treatment up to three treatments. Pretreatment with urea and salicylic acid	75% warts (23% placebo) at 1, 3, 6 and 11 months	[16]
Heat	Placebo, red light	$N=28$ heat, 28 placebo	Infrared light to take skin surface to 44°C. 30 mins per day for 3 consecutive days, repeated 2 weeks later if needed	54% warts (12% placebo) at 3 months	[17]
Maxicalcitol	No	$N=17.13$ children	Maxacalcitol, 25 μg/g ointment. Application 3 times daily	100% at 6 months, 88% by 2 months	[18]
Tretinoin	No	26 children	0.05% cream, applied daily for 6 weeks. Plane warts	85% patients at 12 weeks	[19]
Cidofovir	Nil	7 children	1% cream, daily duration	57% at 12 weeks	[20]
		17 children	Retrospective study. 3% cream, twice daily duration	76% at 32 weeks	[21]
Imiquimod	Nil	$N=37$	5% cream. Application twice daily for up to 24 weeks	27% patients at 24 weeks	[22]
	Nil	$N=15$ Adults	5% cream, 3 times weekly for 8 weeks, daily for 8 weeks, daily with occlusion for 8 weeks. One side only treated. Immunosuppressed transplant recipients	21% treated warts (0% untreated) at 24 weeks	[23]
	Nil	$N=15.3$ children	5% cream application daily for up to 12 weeks. Plane warts	40% patients at 12 weeks	[24]

Table 1 (*Continued*)

Treatment	Comparator	Number	Details of treatment	Clearance rate (comparator)	References
Cimetidine oral	Placebo	*N*=35, 35 placebo	25–40 mg/kg/day for 3 months	32% patients (31%placebo) at 3 months	[25]
	Placebo	*N*=9 cimetidine, 8 placebo. Adults	400 mg bd for 3 months. Plantar warts	0% patients (12% placebo) at 3 months	[26]
	Placebo	*N*=19, 21 placebo	2400 mg/day for 12 weeks	26% patients (5% placebo) at 12 weeks	[27]
Zinc sulphate oral	Placebo, glucose	*N*=40 zinc sulphate, 40 placebo	10 mg/kg daily for 2 months	50% patients (0% placebo) at 2 and 6 months	[28]
	Placebo, starch	*N*=32 zinc sulphate, 23 placebo	10 mg/kg daily for up to 2 months	78% patients (13% placebo) at 2 months	[29]

PDT, photodynamic therapy.

3 times. This treatment has been used with reported success in periungual warts and in immunosuppressed individuals (Table 1). The use of a combination treatment to reduce the wart thickness prior to PDT can make direct comparison impossible.

Heat treatment alone has been reported to be useful in a trial of adults and children (Table 1).

Antiproliferative treatments

Decreasing epidermal turnover may alter the virus life cycle and also often produce an irritant effect.

VITAMIN D ANALOGUES

Calcipotriol and maxacalcitol have been reported as treatment in individual cases or small open studies (Table 1). There is one report of injection of vitamin D directly into warts, which has suggested that this method might produce a useful effect, but with uncontrolled variables, it is not clear if this was a reproducible effect [38].

RETINOIDS

There is evidence for the use of tretinoin cream for plane warts in children although the major side-effect of irritation may be intolerable. (Table 1) Adapalene gel 0.1% has also been used to treat warts in an open study including a few teenage children and adults [39] compared with treatment with fortnightly freezing. The treated warts had 100% clearance rate in each group, with the time to clearance reported as 37 days in the adapalene group and 52 days for cryotherapy. This is a very high clearance rate for cryotherapy compared with other published trials.

Oral retinoid therapy is a not-infrequent treatment in immunosuppressed individuals with extensive warts, and etretinate has been used in children with severely troublesome warts [40]. A recent small placebo-controlled study has again shown effectiveness with 100% clearance in isotretinoin-treated individuals and 0% clearance in the placebo-treated group [41▪▪]. However, the study did not include follow-up data, which is of importance for a treatment that is likely to have its effect via reduced epidermal proliferation.

5-FLUOROURACIL

Fluorouracil, as 5% cream and as 0.5% lotion in combination with 10% salicylic acid, has been used off-license to treat warts. 5-Fluorouracil (5-FU) is an antimetabolite and should only be used over limited areas. It has been used safely to treat warts in children [42] treating up to five warts at a time. Treatment twice daily with 5% 5-FU under occlusion or occlusion alone led to the clearance of 95% 5-FU-treated warts compared with 10% of placebo-treated warts. Other studies, including the combination of weaker 5-FU with salicylic acid, have reported clearance rates nearer 60% [1▪].

PODOPHYLLIN AND PODOPHYLLOTOXIN

Podophyllin and now more commonly the purified active component podophyllotoxin are used regularly for treating ano-genital warts. Under occlusion and after paring or rubbing down, they can have an

effect on keratinized skin warts [1▪], but overenthusiastic application can lead to abscess formation and ulceration. Neither are licensed for use in children.

Antiviral treatments

Two topical preparations in use for decades, formaldehyde and glutaraldehyde, work as virucidal agents, destroying the virus particles and so theoretically could reduce the risk of spread. Neither is supported by strong evidence.

Cidofovir can be classed as antiviral or antiproliferative because of its inhibitory effect on DNA replication. It has a high toxicity when administered intravenously and although this route has been reported for warts [43], there is more interest in topical cidofovir for wart management (Table 1). It is difficult and expensive to obtain cidofovir, making it very unlikely to become a routine treatment for warts.

Immunotherapy

Activation of the immune response against virally infected cells should mimic the process of natural resolution.

IMIQUIMOD

The arrival of a topical immunomodulator in the form of imiquimod cream has sparked a large number of reports and a few trials for its use as an off-license treatment for common warts (Table 1). In a recent study of 86 children, imiquimod cream used with a keratolytic gave similar clearance rates to cryotherapy (81 vs 67%, respectively) but again, no placebo control was used [44]. Overall, the evidence is insufficient [45] to recommend imiquimod as a routine treatment for cutaneous warts.

TOPICAL IMMUNOTHERAPY

Topical immunotherapy for warts is labor-intensive, with a need for adequate sensitization and then repeated treatments which, in a few, can lead to side-effects of widespread urticaria or vitiligo. Most people will tolerate the localized itch and as it is painless, it is an attractive option for children.

Diphenylcyclopropenone [diphencyprone (DPC)] is used most commonly with squaric acid dibutylester (SADBE) as an alternative. Most evaluation of their efficacy has relied on retrospective review or open studies. In an open but physician-blinded study of DPC, which included 72 children and adolescents [46], the complete cure rate was 92% in the pediatric participants. Clearance was significantly quicker in children compared with adults (18 compared with 23 weeks). The cure rate has been high in other open studies [47] with success in difficult to treat sites such as periungual and plantar warts as well as in immunocompromised patients [48,49].

SADBE is an alternative allergen for therapeutic use. It seems to give comparable success, acceptance and safety rates as DPC [50], as well as suffering from a similar lack of placebo-controlled trials.

INTRALESIONAL IMMUNOTHERAPY

There has been a recent rapid increase in the number of publications suggesting intralesional immunotherapy as a potentially efficacious treatment for warts. Candida antigen has been used for some years, usually by injection of the antigen into just one wart, for up to 3 times, with an average of 2–3 injection treatments. In a retrospective review of 170 treated children, 55 were followed up of whom 48 (87%) were found to have complete clearance, whereas only three patients showed no change [51]. In this report, it is not clear if only the injected warts cleared or if any distant lesions also resolved.

Most reported prospective studies have not been placebo controlled, but Khurshid and Pal [52] used isotonic saline injections as placebo in a prospective interventional study of 60 patients involving both children and adults. A reduction in the number of warts was seen in 67% of the Candia-injected patients at 3-month follow-up, whereas only 20% of patients injected with saline had an improvement in wart number. The dropout rate was high (27%).

Two recent retrospective reviews of treated patients have reported intralesional Candida as a safe and reasonably well-tolerated therapy. In one review of pediatric practice, there was a clearance rate of 71% in injected warts in 220 children with 12% of distant warts also responding [53], and in another review of both children and adults, 39% of injected warts completely cleared [54].

Tuberculin purified protein derivative (PPD) and Bacillus Calmette-Guerin have been used as general immunogens for many years, but there has been some recent interest in revisiting this treatment for warts. In an open uncontrolled study, 61 patients received the vaccine intralesionally into a maximum of 10 warts per treatment, with 55 completing treatment and follow-up. There was complete clearance of all warts in 42 of 55 (76%) of patients [55]. In a direct comparison with cryotherapy, the clearance rates were comparable, but a greater number of distant warts cleared in the immunotherapy group [56].

Most recently, measles, mumps and rubella (MMR) vaccine has been used as intralesional immunotherapy. In a retrospective study including children, 136 patients received fortnightly injections to a single wart. Complete response of the treated wart occurred in 26% with the highest response rate occurring in younger participants [57]. In a prospective uncontrolled study of 40 patients of 12 years and over, there was complete clearance in 19 (47%) warts, both treated and distant, [58] but a 15% participant dropout rate. A small placebo-controlled study of PPD, MMR and saline control compared clearance rates of treated and distant warts. Complete clearance was observed in 60, 40 and 0%, respectively [59].

Intralesional injection of a safe antigen is showing promise as a treatment for warts but the lack of adequately sized, properly controlled and blinded studies makes it impossible to endorse this approach as a treatment to be used more widely. It does involve operator training and repeated visits but in that respect is probably comparable in cost (in time, practitioner involvement and financial) with cryotherapy. As with freezing, hypopigmentation has been reported post-therapy [60].

The systemic immune modulator cimetidine has shown no benefit, but initial results of zinc sulphate suggest a possible effect (Table 1).

MOLLUSCUM CONTAGIOSUM

Evidence for efficacy of treatment for molluscum contagiosum is more scanty than that for warts and is often of poor quality. Much practice has been based on anecdotal evidence or open studies, and there are very few published placebo-controlled trials [61]. This relates in part to the difficulty of blinding operative treatments such as surgery or cryotherapy but may also relate to the perceived lack of need for robust evidence for a relatively harmless disease. It should be borne in mind that quality of life is substantially affected in about 10% of children with molluscum contagiosum [62▪▪].

A Cochrane review in 2009 concluded that there was insufficient evidence to suggest superiority of any particular treatment [63], and recent publications have not changed that overall message. Indeed, there is a continuing debate as to whether treatments have any real advantage over no treatment at all [64]. Spontaneous clearance is expected in 70% within 18 months [62▪▪] and may be accompanied by an intense inflammatory reaction [65].

A number of topical treatments, which could be used as home treatments, have at least some evidence behind them and are worth considering. For more severe or troubling infections, more persistent or more aggressive treatments may be considered.

GENERAL MANAGEMENT

For many, who have mild disease or who are not bothered by the lesions, no treatment is probably the best option. It is important to reduce any associated atopic eczema or to reduce the likelihood of molluscum contagiosum-stimulated irritated skin and eczema, which could lead to scratching and spread. Emollients should be used liberally and topical steroids, if needed, sparingly. Within a household, it is advisable to avoid sharing bathtubs, towels, flannels or sponges to reduce the chance of spread between individuals. It may be suggested that swimming should be avoided – this may lead to spread to others, but the importance of learning to swim is almost always greater than the potential harm of catching molluscum.

SURGERY

Some decades ago, almost the only and certainly the most common treatment for molluscum contagiosum in children was curettage. The procedure has become more acceptable since the introduction and use of topical anesthesia [66].

Despite the caveats, the treatment can produce a high level of satisfaction [67]. In a study of 124 children comparing four different treatment approaches to treat a maximum of 10 mollusca in each child, curettage was performed under topical anesthesia, with the addition of systemic sedation if deemed necessary. A total of 81% of the 31 patients had clearance of the 10 curetted lesions after one treatment and 87% of both patients and parents were satisfied with curettage as a treatment. Another study in which all lesions were treated has suggested that most patients will need two or more treatments with curettage for cure [68], and success rate may depend heavily on number and distribution of lesions, skill of the operator and history of atopy or the presence of active atopic dermatitis.

Other surgical procedures have been suggested, involving the extrusion of the central 'core' of each lesion, without curettage of the whole lesion [69]. With patient compliance and good child-operator rapport and technique, this offers an alternative that anecdotally leads to a less traumatic operation and a lower risk of scarring [70].

CRYOTHERAPY

Cryotherapy is probably the treatment of choice for the older child. In a 16-week study in children of weekly freezing compared with imiquimod 5%, complete clearance occurred in 100% (37 of 37) of the cryotherapy group by 6 weeks and in 92% (34 of 37) of the imiquimod group by 12 weeks [71].

IRRITANTS

The only application licensed specifically for the treatment of molluscum contagiosum is potassium hydroxide. This is recently been marketed as a 5% solution (MolluDab, UK) and applied directly to the lesions twice daily for about 1 week or until an inflammatory response develops. Strengths of 10 or 20% potassium hydroxide have also been used in small trials with reported clearance rates of 100% of individuals by 3 months and 60–70% at 1 month [72–74]. The 5% solution seems to produce a slower effect but has a lower chance of adverse reactions such as burning discomfort after applications or postinflammatory hyperpigmentation or hypopigmentation [74]. In a very small placebo-controlled study of 10% KOH, seven out of 10 children cleared within 2 months compared with two out of 10 treated with placebo, but the groups were too small to show statistical significance [75].

Table 2. Molluscum contagiosum treatments not discussed in detail in the text

Treatment	Comparator	Number	Details of treatment	Clearance rate (comparator)	References
Salicylic acid	Placebo, alcohol; phenol	*N*=37, 36 placebo	12% in collodion applied twice per week	88% patients, as treated, (59% placebo) at 6 months	[76]
	Curettage; cantharidin; imiquimod	*N*=30 Children	16.7 and 15% lactic acid in collodion applied 3 times per week	100% lesions clear by second visit	[67]
Nitric oxide	5% salicylic acid cream	*N*=30 total (active + placebo) Children	5% sodium nitrate cream with 5% salicylic acid applied daily for 1–3 months	75% (21% placebo) at 3 months	[77]
Retinoid	Nil	*N*=1, 4 years old	1% adapalene daily	100% lesions at 4 weeks	[78]
	Benzoyl peroxide	*N*=15, 15 benzoyl peroxide	0.05% tretinoin cream applied twice daily for 4 weeks	45% patients (92% benzoyl peroxide) at 6 weeks	[79]
Hydrogen peroxide	Nil	*N*=1, 8 months old	1% cream daily	Clearance after 1 week	[80]
Benz per	Tretinoin	*N*=15, 15 tretinoin	10% benzoyl peroxide cream applied twice daily for 4 weeks	92% patients (45% tretinoin) at 6 weeks	[79]
Plant oil	Olive oil (vehicle)	*N*=15 Children	10% Lemon myrtle oil applied daily	90% reduction in number of lesions (0% placebo) at 3 weeks	[81]
Ingenol mebutate	Nil	*N*=1, 4 years old	0.015% ingenol mebutate cream applied daily for 3 days, repeated	100% lesions clear at 1 month	[82]
Phenol	Physical expression	*N*=14, 52 lesions	Total of 52 lesions treated with liquefied phenol once	75% of lesions (77% physical expression) at 1 month	[70]
	Placebo, alcohol; 12% salicylic acid	*N*=41, 36 placebo	10% phenol in alcohol applied monthly	56% patients, as treated, (59% placebo) at 6 months	[76]
Trichloroacetic acid	Nil	Many	20–35% trichloroacetic acid applied with pointed tip applicator	Good response	[83]
IL Candida antigen	Nil	*N*=29 Children	1–3 lesions injected per treatment; up to six treatments. Retrospective	55% patients, local and distant lesions	[84]
	Nil	*N*=47 Children	1–2 lesions injected per treatment, monthly treatment. Only 25 followed up. Retrospective	56% patients, local and distant lesions	[51]

Other irritant applications such as salicylic acid and nitric oxide have been evaluated in placebo-controlled trials, and there is scanty evidence for other irritants. Caustics and acids are also used, but with weak evidence (Table 2) [67,70,76–84,51].

Cantharidin has been widely used in North America [85] but less in Europe. Applied carefully to individual lesions as 0.7% cantharidin in collodion base (Cantharone and Canthacur), it is not painful at the time of application, but leads to blister formation and often later discomfort because of the inflammation and erosion. The vesicant is applied carefully to the center of the lesion without contamination of surrounding skin.

In the comparative study by Hanna *et al.* [67], 37% of the 30 patients treated cleared the 10 treated lesions after a single treatment, and a further 43% after two treatments, whereas 20% of patients needed three or more treatments. Other reported rates of clearance in retrospective studies are up to 90% after an average of two treatments [86]. There is a small risk of postinflammatory hyperpigmentation.

There is considerable variation between protocols for cantharidin use, and therefore the efficacy of treatment, but most practitioners do not occlude the lesions after application and advise washing the area 4–6 h later [85,87,88]. Retrospective reviews of patients treated with cantharidin report a high level of satisfaction with the treatment [67,84,87], suggesting that it is both tolerable and effective.

In contrast, a recent study and the first double-blind, placebo-controlled trial of cantharidin for molluscum contagiosum has shown no significant difference in the clearance rates of cantharidin treatment compared with placebo. Over 8 weeks, cantharidin 0.7% ($n = 13$) or its collodion base ($n = 16$) was applied to up to 20 lesions on each visit every 1–2 weeks to a maximum of 8 weeks. Children treated with cantharidin showed a slightly greater reduction in total lesion count at the end of the 2 months, but lesion number reduced in both groups. As the authors themselves suggest, a longer treatment period might have revealed greater differences [89▪▪].

IMMUNOTHERAPY

Imiquimod cream 5%, originally licensed for the treatment of genital warts, initially suggested a useful effect in molluscum contagiosum with clearance rates of 33–92% reported [71,90]. However, larger unpublished studies suggest that the treatment is no better than placebo [91▪▪]. Currently, imiquimod cannot be recommended as a routine treatment for molluscum.

In an open study of weekly DPC in acetone in 22 children with molluscum contagiosum, 64% cleared by 8 weeks [92]. There was an 18% dropout because of side-effects of itching and erythema.

Treatment with intralesional candida antigen has produced some success (Table 2), and the MMR vaccine has also been used in two cases [93].

LASER

The pulsed dye laser has been used in two recent series to treat mollusca in a total of 34 children and gave 84 or 99% clearance after a single treatment [94,95]. Topical local anesthetic was felt to be needed in only nine of the 34 patients.

OTHER TREATMENTS

In long-term immune compromise, mollusca can become widespread or giant. In these situations, a number of more aggressive treatments including topical or intravenous cidofovir and paclitaxel have been tried, and individual case or small group successes are reported recently [96–99].

CONCLUSION

Strong evidence to support many of the treatments in common use for warts or molluscum contagiosum has been lacking, but there is now more reason to endorse the use of salicylic acid, cryotherapy and both topical and intralesional immunotherapy for warts. The commonly used treatments for molluscum contagiosum, cantharidin and imiquimod now have evidence to suggest less efficacy than previously thought.

Acknowledgements

None.

Financial support and sponsorship

None.

Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ▪ of special interest
- ▪▪ of outstanding interest

1. Sterling JC, Gibbs S, Haque Hussain SS, *et al.* British Association of ▪ Dermatologists' guidelines for the management of cutaneous warts. Br J Dermatol 2014; 171:696–712.

Recent review of all currently used treatments for cutaneous warts.

2. Kwok CS, Gibbs S, Bennett C, *et al.* Topical treatments for cutaneous warts. Cochrane Database Syst Rev 2012; 9:CD001781.
3. Kuwabara AM, Rainer BM, Basdag H, Cohen BA. Children with warts: a retrospective study in an outpatient setting. Pediatr Dermatol 2015; 32: 679–683.

4. 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 Tech Assess 2006; 10:25.
5. 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; 165:233–246.
6. 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; 182:1624–1630.
7. Bart BJ, Biglow J, Vance JC, Neveaux JL. Salicylic acid in karaya gum patch as a treatment for verruca vulgaris. J Am Acad Dermatol 1989; 20:74–76.
8. Banihashemi M, Pezeshkpoor F, Yazdanpanah MJ, Family S. Efficacy of 80% phenol solution in comparison with cryotherapy in the treatment of common warts of the hands. Singapore Med J 2008; 49:1035–1037.
9. Kartal Durmazlar SP, Atacan D, Eskioglu F. Cantharidin treatment for recalcitrant facial flat warts: a preliminary study. J Dermatolog Treat 2009; 20:114–119.
10. Bhat RM, Vidya K, Kamath G. Topical formic acid puncture technique for the treatment of common warts. Int J Dermatol 2001; 40:415–419.
11. Dhar SB, Rashid MM, Islam A, Bhuiyan M. Intralesional bleomycin in the treatment of cutaneous warts: a randomized clinical trial comparing it with cryotherapy. Ind J Dermatol Venereol Leprol 2009; 75:262–267.
12. Munkvad M, Genner J, Staberg B, Kongsholm H. Locally injected bleomycin in the treatment of warts. Dermatologica 1983; 167:86–89.
13. Sardana K, Garg V, Relhan V. Complete resolution of recalcitrant periungual/subungual wart with recovery of normal nail following 'prick' method of administration of bleomycin 1%. Dermatol Ther 2010; 23:407–410.
14. 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; 21:1170–1174.
15. 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; 355:963–966.
16. 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; 61:30–34.
17. 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; 201:1169–1172.
18. Imagawa I, Suzuki H. Successful treatment of refractory warts with topical vitamin D3 derivative (maxacalcitol, 1alpha, 25-dihydroxy-22-oxacalcitriol) in 17 patients. J Dermatol 2007; 34:264–266.
19. Kubeyinje EP. Evaluation of the efficacy and safety of 0.05% tretinoin cream in the treatment of plane warts in Arab children. J Dermatol Treat 1996; 7:21–22.
20. Field S, Irvine AD, Kirby B. The treatment of viral warts with topical cidofovir 1%: our experience of seven pediatric patients. Br J Dermatol 2009; 160:223–224.
21. Fernández-Morano T, del Boz J, González-Carrascosa M, *et al.* Topical cidofovir for viral warts in children. JEADV 2011; 25:1487–1489.
22. Grussendorf-Conen EI, Jacobs S, Rubben A, *et al.* Topical 5% imiquimod long-term treatment of cutaneous warts resistant to standard therapy modalities. Dermatology 2002; 205:139–145.
23. Harwood CA, Perrett CM, Brown VL, *et al.* Imiquimod cream 5% for recalcitrant cutaneous warts in immunosuppressed individuals. Br J Dermatol 2005; 152:122–129.
24. Kim MB, Ko HC, Jang HS, *et al.* Treatment of flat warts with 5% imiquimod cream. J Eur Acad Dermatol 2006; 20:1349–1350.
25. Yilmaz E, Alpsoy E, Basaran E. Cimetidine therapy for warts: a placebo-controlled, double-blind study. J Am Acad Dermatol 1996; 34:1005–1007.
26. Lee SH, Rose B, Thompson CH, Cossart Y. Plantar warts of defined aetiology in adults and unresponsiveness to low dose cimetidine. Australasian J Dermatol 2001; 42:219–222.
27. 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; 41:123–127.
28. Al-Gurairi FT, Al-Waiz M, Sharquie KE. Oral zinc sulfate in the treatment of recalcitrant viral warts: randomized placebo-controlled clinical trial. Br J Dermatol 2002; 146:423–431.
29. 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; 60:706–708.
30. Bruggink SC, Gussekloo J, Egberts PF, *et al.* Monochloroacetic acid application is an effective alternative to cryotherapy for common and plantar warts in primary care: a randomized controlled trial. J Invest Dermatol 2015; 135:1261–1267.
31. Shahmoradi Z, Assaf F, Al Said H, *et al.* Topical pyruvic acid (70%) versus topical salicylic acid (16.7%) compound in treatment of plantar warts: a randomized controlled trial. Adv Biomed Res 2015; 4:113.
32. Veien NK, Madsen SM, Avrach W, *et al.* The treatment of plantar warts with a keratolytic agent and occlusion. J Dermatol Treat 1991; 2:59–61.
33. de Haen M, Spigt MG, van Uden CJ, *et al.* Efficacy of duct tape vs placebo in the treatment of verruca vulgaris (warts) in primary school children. Arch Pediatr Adolesc Med 2006; 160:1121–1125.
34. 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; 143:309–313.
35. 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.
36. van Brederode RL, Engel ED. Combined cryotherapy/70% salicylic acid treatment for plantar verrucae. J Foot Ankle Surg 2001; 40:36–41.
37. Sparreboom EE, Luijks HG, Luiting-Welkenhuyzen HA, *et al.* Pulsed-dye laser treatment for recalcitrant viral warts: a retrospective case series of 227 patients. Br J Dermatol 2014; 171:1270–1273.
38. Aktaş H, Ergin C, Demir B, Ekiz Ö. Intralesional vitamin D injection may be an effective treatment option for warts. J Cutan Med Surg 2016; 20:118–122.
39. Gupta R, Gupta S. Topical adapalene in the treatment of plantar warts; randomized comparative open trial in comparison with cryo-therapy. Indian J Dermatol 2015; 60:102.
40. Gelmetti C, Cerri D, Schiuma AA, *et al.* Treatment of extensive warts with etretinate; a clinical trial in 20 children. Pediatr Dermatol 1987; 4:254–258.
41. ■■ Olguin-García MG, Jurado-Santa Cruz F, Peralta-Pedrero ML, Morales-Sánchez MA. A double-blind, randomized, placebo-controlled trial of oral isotretinoin in the treatment of recalcitrant facial flat warts. J Dermatolog Treat 2015; 26:78–82.

A useful addition to the few placebo-controlled trials for wart treatments.

42. Gladsjo JA, Alio Sáenz AB, Bergman J, *et al.* 5% 5-fluorouracil cream for treatment of verruca vulgaris in children. Pediatr Dermatol 2009; 26:279–285.
43. 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; 25:387–389.
44. Stefanaki C, Lagogiani I, Kouris A, *et al.* Cryotherapy versus imiquimod 5% cream combined with a keratolytic lotion in cutaneous warts in children: a randomized study. J Dermatolog Treat 2016; 27:80–82.
45. Ahn CS, Huang WW. Imiquimod in the treatment of cutaneous warts: an evidence-based review. Am J Clin Dermatol 2014; 15:387–399.
46. Kang HS, Lee MW, Paek JO, *et al.* Comparison of cure rates and durations of treatment with diphenylcyclopropenone immunotherapy for warts in children/adolescents and adults. Int J Dermatol 2014; 53:1293–1298.
47. Suh D-W, Lew B-L, Sim W-Y. Investigations of the efficacy of diphenylcyclopropenone immunotherapy for the treatment of warts. Int J Dermatol 2014; 53:e567–e571.
48. Choi Y, Kim do H, Jin SY, *et al.* Topical immunotherapy with diphenylcyclopropenone is effective and preferred in the treatment of periungual warts. Ann Dermatol 2013; 25:434–439.
49. Audrain H, Siddiqui H, Buckley DA. Diphencyprone immunotherapy for viral warts in immunosuppressed patients. Br J Dermatol 2013; 168:1138–1139.
50. Pandey S, Wilmer EN, Morrell DS. Examining the efficacy and safety of squaric acid therapy for treatment of recalcitrant warts in children. Pediatr Dermatol 2015; 32:85–90.
51. Maronn M, Salm C, Lyon V, Galbraith S. One-year experience with Candida antigen immunotherapy for warts and molluscum. Pediatr Dermatol 2008; 25:189–192.
52. Khurshid K, Pal SS. Role of Candida antigen in treatment of viral warts: a placebo-controlled study. J Pakistani Assoc Dermatol 2009; 19:146–150.
53. Muñoz Garza FZ, Roé Crespo E, Torres Pradilla M, *et al.* Intralesional Candida antigen immunotherapy for the treatment of recalcitrant and multiple warts in children. Pediatr Dermatol 2015; 32:797–801.
54. Alikhan A, Griffin JR, Newman CC. Use of Candida antigen injections for the treatment of verruca vulgaris: a two-year mayo clinic experience. J Dermatolog Treat 2015; 1–4.
55. Saoji V, Lade NR, Gadegone R, Bhat A. Immunotherapy using purified protein derivative in the treatment of warts: an open uncontrolled trial. Indian J Dermatol Venereol Leprol 2016; 82:42–46.
56. Dhakar AK, Dogra S, Vinay K, *et al.* Intralesional Mycobacterium w vaccine versus cryotherapy in treatment of refractory extragenital warts: a randomized, open-label, comparative study. J Cutan Med Surg 2016; 20:123–129.
57. Na CH, Choi H, Song SH, *et al.* Two-year experience of using the measles, mumps and rubella vaccine as intralesional immunotherapy for warts. Clin Exp Dermatol 2014; 39:583–589.
58. Saini P, Mittal A, Gupta LK, *et al.* Intralesional mumps, measles and rubella vaccine in the treatment of cutaneous warts. Indian J Dermatol Venereol Leprol 2016; 82:343–345.
59. Shaheen MA, Salem SA, Fouad DA, El-Fatah AA. Intralesional tuberculin (PPD) versus measles, mumps, rubella (MMR) vaccine in treatment of multiple warts: a comparative clinical and immunological study. Dermatol Ther 2015; 28:194–200.
60. Wilmer EN, Burkhart CN, Merrell DS. Goodbye warts, hello vitiligo: Candida antigen-induced depigmentation. Pediatr Dermatol 2013; 30:e214–e215.
61. Brown J, Janniger CK, Schwartz RA, Silverberg NB. Childhood molluscum contagiosum. Int J Dermatol 2006; 45:93–99.
62. ■■ Olsen JR, Gallacher J, Finlay AY, *et al.* Time to resolution and quality of molluscum contagiosum in children in the UK: a prospective community cohort study. Lancet Inf Dis 2014; 15:190–195.

This study gives useful data on the epidemiology of molluscum contagiosum infection in the community.

63. van der Wouden JC, van der Sande R, van Suijlekom-Smit LW, *et al.* Interventions for cutaneous molluscum contagiosum. Cochrane Database Syst Rev 2009; 4:CD004767.

64. Basdag H, Rainer BM, Cohen BA. Molluscum contagiosum: to treat or not to treat? Experience with 170 children in an outpatient clinic setting in the Northeastern United States. Pediatr Dermatol 2015; 32:353–357.

65. Vermi W, Fisogni S, Salogni L, *et al.* Spontaneous regression of highly immunogenic molluscum contagiosum virus (MCV)-induced skin lesions is associated with plasmacytoid dendritic cells and IFN-DC infiltration. J Invest Dermatol 2011; 131:426–434.

66. Rönnerfält L, Fransson J, Wahlgren CF. EMLA cream provides rapid pain relief for the curettage of molluscum contagiosum in children with atopic dermatitis without causing serious application-site reactions. Pediatr Dermatol 1998; 15:309–312.

67. Hanna D, Hatami A, Powell J, *et al.* A prospective randomized trial comparing the efficacy and adverse effects of four recognized treatments of molluscum contagiosum in children. Pediatr Dermatol 2006; 23:574–579.

68. Simonart T, De Maertelaer. Curettage treatment for molluscum contagiosum: a follow-up survey study. Br J Dermatol 2008; 159:1144–1147.

69. Martin-Garcia RF, Garcia ME, Rosado A. Modified curettage technique for molluscum conrtagiosum. Pediatr Dermatol 2007; 24:192–194.

70. Weller R, O'Callaghan CJ, MacSween RM, *et al.* Scarring in molluscum contagiosum: comparison of physical expression and phenol ablation. Br Med J 1999; 319:1540.

71. Al-Mutairi N, Al-Doukhi A, Al-Farag S, Al-Haddad A. Comparative study on the efficacy, safety, and acceptability of imiquimod 5% cream versus cryotherapy for molluscum contagiosum in children. Pediatr Dermatol 2010; 27:388–394.

72. Romiti R, Ribero AP, Grinblat BM, *et al.* Treatment of molluscum contagiosum with potassium hydroxide: a clinical approach in 35 children. Pediatr Dermatol 1999; 16:228–231.

73. Romiti R, Ribeiro AP, Romiti N. Evaluation of the effectiveness of 5% potassium hydroxide for the treatment of molluscum contagiosum. Pediatr Dermatol 2000; 17:495.

74. Vijay A, Gupta ML, Dalela G, Sharma MK. Comparative study of efficacy and side effects of 10% and 20% koh aqueous solution for treatment of molluscum contagiosum in children. Int J Biol Med Res 2012; 3:2497–2501.

75. Short KA, Fuller LC, Higgins EM. Double-blind, randomized, placebo-controlled trial of the use of topical 10% potassium hydroxide solution in the treatment of molluscum contagiosum. Pediatr Dermatol 2006; 23:279–281.

76. Leslie KS, Dootson G, Sterling JC. Topical salicylic acid gel as a treatment for molluscum contagiosum in children. J Dermatol Treat 2005; 16:336–340.

77. Ormerod AD, White MI, Shah SA, *et al.* Molluscum contagiosum effectively treated with a topical acidified nitrite, nitric oxide liberating cream. Br J Dermatol 1999; 141:1051–1053.

78. Scheinfeld N. Treatment of molluscum contagiosum: a brief review and discussion of a case successfully treated with adapelene. Dermatol Online J 2007; 13:15.

79. Saryazdi S. The comparative efficacy of benzoyl peroxide 10% cream and tretinoin 0.05% cream in the treatment of molluscum contagiosum. Pediatric Dermatol 2004; 21:399.

80. Semkova K, Palamaras I, Robles W. Hydrogen peroxide 1% cream under occlusion for treatment of molluscum contagiosum in an 8-month-old infant: an effective and safe treatment option. Clin Exp Dermatol 2014; 39: 560–561.

81. Burke BE, Baillei J, Olson RD. Essential oil of Australian lemon myrtle (*Backhousia citriodora*) in the treatment of molluscum contagiosum in children. Biomed Pharmacother 2004; 58:245–247.

82. Javed S, Tyring SK. Treatment of molluscum contagiosum with ingenol mebutate. J Am Acad Dermatol 2014; 70:e105.

83. Bard S, Shiman MI, Bellman B, Connelly EA. Treatment of facial molluscum contagiosum with trichloroacetic acid. Pediatr Dermatol 2009; 26:425–426.

84. Enns LL, Evans MS. Intralesional immunotherapy with Candida antigen for the treatment of molluscum contagiosum in children. Pediatr Dermatol 2011; 28:254–258.

85. Coloe J, Morrell DS. Cantharidin use among pediatric dermatologists in the treatment of molluscum contagiosum. Pediatr Dermatol 2009; 26:405–408.

86. Silverberg NB, Sidbury R, Mancini AJ. Childhood molluscum contagiosum: experience with cantharidin therapy in 300 patients. J Am Acad Dermatol 2000; 43:503–507.

87. Moye VA, Cathcart S, Morrell DS. Safety of cantharidin: a retrospective review of cantharidin treatment in 405 children with molluscum contagiosum. Pediatr Dermatol 2014; 31:450–454.

88. Mathes EFD, Frieden IJ. Treatment of molluscum contagiosum with cantharidin: a practical approach. Pediatr Ann 2010; 39:124–128.

89. ■■ Coloe Dosal J, Stewart PW, Lin J-A, *et al.* Cantharidin for the treatment of molluscum contagiosum: a prospective, double-blinded, placebo-controlled trial. Pediatr Dermatol 2014; 31:440–449.

A well-conducted study that calls into question the widespread use and effectiveness of cantharidin.

90. Theos AU, Cummins R, Silverberg NB, Paller AS. Effectiveness of imiquimod cream 5% for treating childhood molluscum contagiosum in a double-blind, randomized pilot trial. Cutis 2004; 74:134–138.

91. ■■ Katz KA. Dermatologists, imiquimod, and treatment of molluscum contagiosum in children: righting wrongs. JAMA Dermatol 2015; 151:125–126.

By accessing nonpublished studies, this review illustrates the error of adoption of a treatment on poor evidence.

92. Kang SH, Lee D, Hoon Park J, *et al.* Treatment of molluscum contagiosum with topical diphencyprone therapy. Acta Derm Venereol 2005; 85:529–530.

93. Na CH, Kim DJ, Kim MS, *et al.* Successful treatment of molluscum contagiosum with intralesional immunotherapy by measles, mumps, and rubella vaccine: a report of two cases. Dermatol Ther 2014; 27:373–376.

94. Binder B, Weger W, Komericki P, *et al.* Treatment of molluscum contagiosum with a pulsed dye laser: pilot study with 19 children. J Dtsch Dermatol Ges 2008; 6:121–125.

95. Omi T, Kawana S. Recalcitrant molluscum contagiosum successfully treated with the pulsed dye laser. Laser Ther 2013; 22:51–54.

96. Toro JR, Wood LV, Patel NK, *et al.* Topical cidofovir: a novel treatment for recalcitrant molluscum contagiosum in children infected with human immunodeficiency virus 1. Arch Dermatol 2000; 136:983–985.

97. Erickson C, Driscoll M, Gaspari A. Efficacy of intravenous cidofovir in the treatment of giant molluscum contagiosum in a patient with human immunodeficiency virus. Arch Dermatol 2011; 147:652–654.

98. Sisneros SC. Recalcitrant giant molluscum contagiosum in a patient with advanced HIV disease: eradication of disease with paclitaxel. Top HIV Med 2010; 18:169–172.

99. Nguyen HP, Franz E, Stiegel KR, *et al.* Treatment of molluscum contagiosum in adult, pediatric, and immunodeficient populations. J Cutan Med Surg 2014; 18:299–306.