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Treating common warts

Options and evidence

Background
Nongenital warts are a common condition seen in general practice, affecting patients of all ages. There are many treatment options and patients often self medicate with remedies from folklore or tradition before presenting to their doctor.

Objective
This article attempts to summarise the quality of different treatments and to provide recommendations and a quick reference for treating common warts.

Discussion
Many common warts will resolve spontaneously but others are recalcitrant and often require ongoing treatment beyond first line measures. Without definite guidelines for treating recalcitrant warts, it is important for the general practitioner to consider the available evidence for efficacy and contraindication of the various treatment options.

Keywords: warts; skin diseases; treatment; salicylic acid; cryosurgery

Nongenital cutaneous warts are commonly seen in general practice with an overall prevalence of 7–10%[1] and a peak age of presentation of 12–16 years.[1–2] They are most commonly found on the hands and feet but can also be found on the face, eyelids and torso. The causative agent is human papilloma virus (HPV). Without treatment, one-third of cutaneous warts will resolve spontaneously within 3 months and two-thirds within 2 years.[3] Myrmecia warts often persist despite repeated treatments and become recalcitrant warts. There is no consensus on the prevalence of, and most effective treatment for, recalcitrant warts.

Classification of nongenital cutaneous warts

There are over 100 identified types of HPV;[4] the most common types of cutaneous warts are type 1, 2, 3, 4, 7, 10, 27 and 57.[2,4] Cutaneous warts can present in various forms and sizes. An excellent review has been written by Jablonska et al;[5] and a brief summary of the various types of common warts is given in *Table 1* (*Figure 1–4*).

Pathogenesis

With a minor breach in the epithelial surface, HPV enters the epithelial cells via putative surface receptors and proliferates. This results in persistent viral infection with metaplasia of keratinocytes, which gradually accumulate keratohyalin granules[6] and are sloughed off.[4] As these virally infected keratinocytes are not destroyed, the HPV virions are rarely exposed to the Langerhans cells of the skin, and therefore evade being cleared by systemic immunity. This facilitates the viral persistence and continual growth of the wart.

Diagnostic features and differential diagnoses

Cutaneous warts often present as localised flat or dome shaped papules with well demarcated edges. Histological findings include epidermal acanthosis, papillomatosis, hyperkeratosis and parakeratosis with elongated rete ridges often curving toward the centre of the wart.

Figure 1. Myrmecia warts on the ball of calcaneum. These are painful. Notice the typical round appearance with pitting when keratinised plates were removed

Capillary vessels are often prominent and may be thrombosed, giving the pathognomonic brown dots at the centre of the lesion when the warts are pared down. Due to the continuous viral induced hyperkeratotic changes, the surface papillary lines of the skin are disrupted resulting in a rough surface. Most lesions are of skin colour but can appear black due to thrombosed capillaries which are used to feed the wart. While most cutaneous warts tend to be exophytic and painless (ie. grow out of and above the skin), those affecting the palm and soles are often endophytic (ie. grow inwards into the skin) and lead to pain and discomfort. When several warts with different morphologies cluster together, a mosaic wart is formed.[4] Due to the myriad of morphologies and wide area of possible distribution, cutaneous warts have to be differentiated from other skin conditions such as seborrhoeic keratosis, callous, lichen planus, molluscum contagiosum, mole, melanoma, keratoacanthoma and cutaneous horn.[7]

Figure 2. Common warts on the sole of the foot with irregular hyperkeratosis. These are relatively painless

Figure 3. Butcher's wart from a food handler with the exophytic cauliflower morphology on the lateral aspect of the digit. Notice the coexistence of plane warts on the dorsum and base of the finger

Figure 4. Multiple plane warts on dorsum of hand. Notice the papular appearance which can be smooth or hyperkeratotic

Treatment options

Most cutaneous warts are self limiting and resolve within 2 years. When they pose discomfort or aesthetic problems, patients often seek treatment. With a record of existence going back to the ancient Greeks and Romans, the common wart in no way lacks curative options, including hypnotherapy;[8] garlic;[9] duct tape;[7] fig tree latex;[10] oral zinc sulphate;[11] oral histamine 2 receptor antagonist;[11] cautery;[7] hyfrecation;[7] surgical removal;[12] salicylic acid;[2,7] liquid nitrogen cryotherapy;[7] local hyperthermia;[13] CO_2 laser;[3] YAG laser;[12] pulsed dye laser;[14] intense pulsed light (IPL);[15] topical imiquimod;[16] topical 5-fluorouracil;[17] squaric acid;[18] intralesional injection of bleomycin;[19] interferon;[2] candida antigen 1;[20] measles, mumps and rubella (MMR) vaccine;[21] and autoimplantation of wart materials.[22] Detail of each treatment modality is beyond the scope of this article and readers are referred to Lipke's excellent reviews.[7] Classification of quality of evidence (*Table 2*)

Table 1. Categories of common warts with their HPV subtypes

Type	HPV type	Morphology	Mode of regression
Myrmecia warts (*Figure 1*)	1	Round keratinised lesions found commonly on pressure point of foot, often painful endophytic growth with central pit when central hyperkeratotic plate removed	Vascular extravasation and haemorrhage with minimal inflammatory infiltrate
Common warts (*Figure 2*)	2, 4, 57	Flat or raised papules or nodules with irregular hyperkeratotic surfaces commonly found on dorsum of hand and periungually, and can involve the sole of the foot or face – often painless. Lesions can converge to form mosaic warts and can be endophytic	Cellular inflammatory infiltrate involving the lymphocytes, natural killer cells and macrophages
Butcher's warts (*Figure 3*)	7	Found exclusively in butchers and meat handlers, cauliflower-like exophytic lesions found on both sides of the hand but rarely periungually	Vascular extravasation and minimal inflammation
Plane warts (*Figure 4*)	3, 10	Multiple flat papules with relatively smooth but hyperkeratotic surfaces found on the hand and face, often painless and brought on by Koebner phenomenon	Simultaneous inflammatory infiltration of mononuclear cells
Intermediate warts	10, 27	Intermediate morphology between common and plane warts found mostly on dorsum of hands in the immunosuppressed	Simultaneous inflammatory reaction

and recommendations (*Table 3*) according to the United States Preventive Services Task Force are applied to a summary of treatment options and evidence in *Table 4*.

Fresh warts

For lesions that on initial presentation have mild or no symptoms, the general practitioner can choose to observe the 'one-third disappear in 3 months and two-thirds disappear in 2 years' rule. Should the wart persist, the best initial treatment is salicylic acid (evidence I-A), which has clear evidence of advantage over placebo. Next in line would be cryotherapy with liquid nitrogen (evidence I-B), which has not been shown to be superior over other treatments such as salicylic acid or placebo. Liquid nitrogen may have better efficacy than salicylic acid for plantar warts and should be used with caution for lesions around the eye. When patients present with common warts it is likely they have already tried salicylic acid or even liquid nitrogen at home with no result. In such cases, the GP can pursue more aggressive liquid nitrogen cryotherapy, which has longer contact time with paring down to the base and increased risks of pain and blistering. Intralesional immunotherapy or chemotherapy, laser and electrosurgery are better reserved as second line treatments and are not recommended for common warts at initial presentation.

Table 2. Classification of quality of evidence

Level of evidence	Quality of evidence
Level I	Evidence obtained from at least one properly designed randomised controlled trial (RCT)
Level II-1	Evidence obtained from well designed controlled trials without randomisation
Level II-2	Evidence obtained from well designed cohort or case control analytic studies, preferably from more than one centre or research group
Level II-3	Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled trials might also be regarded as this type of evidence
Level III	Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees

Adapted from United States Preventive Services Task Force. Available at www.ahrq.gov/clinic/uspstfix.htm

Table 3. Recommendations: United States Preventive Services Task Force

Level	Recommendations
Level A	Good scientific evidence suggests that the benefits of the clinical service substantially outweigh the potential risks. Clinicians should discuss the service with eligible patients
Level B	At least fair scientific evidence suggests that the benefits of the clinical service outweigh the potential risks. Clinicians should discuss the service with eligible patients
Level C	At least fair scientific evidence suggests that there are benefits provided by the clinical service, but the balance between benefits and risks are too close for making general recommendations. Clinicians need not offer it unless there are individual considerations
Level D	At least fair scientific evidence suggests that the risks of the clinical service outweigh the potential benefits. Clinicians should not routinely offer the service to asymptomatic patients
Level I	Scientific evidence is lacking, of poor quality, or is conflicting, such that the risk versus benefit balance cannot be assessed. Clinicians should help patients understand the uncertainty surrounding the clinical service

Adapted from United States Preventive Services Task Force. Available at www.ahrq.gov/clinic/pocketgd09/gcp09app.htm#ApA

Best practice for treating fresh common warts

Nonfacial lesions are best treated with a salicylic acid gel, cream or instant dry film preparation. Commercial brands come in various strengths from 15–40%. Apply on alternate days with contact time of 8 hours, adding occlusive dressing (adhesive bandage or plastic wrap) if necessary to enhance effects. If no improvement is observed after 6 weeks, proceed to liquid nitrogen application with four sets of five freeze-thaw cycles per treatment, to be repeated fortnightly. Lesions with hyperkeratinisation should either be pared down with a scalpel or rubbed with a pumice stone in warm water before treatment.

For facial lesions, salicylic acid application is not recommended because of the possibility of scarring. They are best treated in the practice with liquid nitrogen. Apply the liquid nitrogen with a fine nozzle spray or cottonwool tip with two sets of five freeze-thaw cycles to be repeated fortnightly. If lesions do not resolve within 3 months, or after five rounds of liquid nitrogen treatment, the warts are considered refractory or recalcitrant.

Lesions that are resolved with initial treatments can recur and they are treated as fresh lesions, albeit with a lower chance of success.

Lesions with unusual morphology, bleeding or pigmentation should be biopsied to exclude possible malignancy.

Recalcitrant warts

When warts fail to resolve after repeated treatments, they are considered recalcitrant. There is no consensus for the definition of recalcitrant warts but as a general rule, they can be described

as warts that fail five rounds of first line treatment (salicylic acid or liquid nitrogen). Plantar warts are notorious for becoming recalcitrant. Certain immunosuppressed conditions create a higher risk of developing recalcitrant warts, these include acute leukemia,[25] organ transplant[26,27] and human immunodeficiency virus infections.[28]

There are no definite guidelines for treating recalcitrant warts and available options include destruction treatments (eg. laser and electrosurgery), intralesional chemotherapy (eg. bleomycin and 5-fluorouracil) and intralesional immunotherapy (eg. interferon and MMR vaccine). These are not first line treatments for common warts and should be administered only with prior training or in a specialist centre so that possible side effects can be monitored. A preferred option of the author is

Table 4. Summary of treatment and evidence for common warts

Method	Level of evidence	Comments
Salicylic acid[2]	I-A	Benefits are established as compared to placebo but only modest. Most trials look at use of salicylic acid in combination with other agents
Liquid nitrogen cryotherapy[2,23]	I-B	Overall evidence is inconclusive to suggest a therapeutic advantage of cryotherapy over other topical treatments or placebo. Aggressive cryotherapy may be more effective but is offset by more pain and blistering
Intralesional interferon[2,23]	I-C	Trials use various forms of interferons (alfa, beta, gamma). Intralesional injections are often painful and overall evidence of use is insufficient
Intralesional bleomycin	I-C	Cochrane review of trials used various dosages and concentrations with different delivery systems, but none show sufficient evidence of beneficial use[2]
	I-B	More recent studies showed significant benefits as compared to cryotherapy[19]
Intralesional candida antigen[1,20]	II-3B	Data from case series and isolated reports. No RCT yet. Suggested use in the more recalcitrant types of warts
Intralesional MMR vaccine[21]	I-B	One RCT and one time series executed with recalcitrant plantar warts. Efficacy for other types of warts still unknown
Autoimplantation of wart material[22]	II-3C	Only one intention-to-treat series reported significant effects. No RCT available
Topical 5-fluorouracil[2]	I-C	Efficacy significant with one study using cream preparation in children, but overall evidence becomes limited when pooled with other studies
Intralesional 5-fluorouracil[24]	I-B	One double blind RCT using a 5-fluorouracil mixture of epinephrine and lidocaine
Topical podophyllin[7]	II-2D	Good efficacy from older case series in 1970s, not recommended now for toxicities. No known RCT
Topical imiquimod[16]	II-2C	Approved for use in genital warts, only two case studies of efficacy for plantar warts. Evidence is still lacking
Topical squaric acid[18]	II-3C	Intention to treat studies showed efficacy in children and cases of recalcitrant wart, known risks of contact dermatitis
Duct tape[2]	I-I	Perhaps the most controversial of all treatments, modest efficacy from an RCT in school children is later refuted by another RCT in adults. Evidence is too conflicting to suggest benefit
Laser (CO_2 and YAG)[14]	I-C	Good efficacy from intention to treat case series especially with recalcitrant warts and in children. The only RCT does not show evidence of benefit over conventional treatment
Intense pulsed light[15,30]	I-I	One case study combines photosensitiser with IPL and shows efficacy, another RCT using IPL alone shows no efficacy. Evidence is lacking
Electrosurgery (electrodessication, electrocoagulation and cautery)[7]	II-1C	Good efficacy from case reports with known risks of scarring and deep tissue damage. One controlled trial compares electrocoagulation with infrared coagulation with no difference, no known RCT. Often used for recalcitrant warts
Surgical excision[7]	II-3D	No RCTs so far, generally not recommended as first line treatment due to scarring, pain and high rate of recurrence – up to 30%

electrodessication (hyfrecation) of the lesion under local anaesthesia, which often results in clearance after a single treatment. However, this option is contraindicated in patients with poor wound healing (eg. uncontrolled diabetes or peripheral vascular diseases), keloid tendency or patients with pace makers. It is also not recommended for lesions on the face.

Best practice for treating recalcitrant warts

Destructive options include aggressive cryotherapy (maximum paring down with scalpel and longer freezing time of 6 seconds instead of the usual 3 seconds), hyfrecation with local anaesthesia, laser treatment and thermocoagulation.

Subject to availability 5-fluorouracil or bleomycin can be administered either topically or intralesionally, preferably in a specialist setting.

Lesions with unusual morphology, bleeding or pigmentation should be biopsied to exclude possible malignancy.

Summary

Common nongenital warts are common and may persist despite active treatment. Salicylic acid is the best evidence based treatment for warts on initial presentation and can be complemented by liquid nitrogen cryotherapy. For recalcitrant warts, choices vary depending on availability and the training of the GP. The expected efficacy must be balanced against costs and possible side effects. It is advisable to perform skin biopsy for suspicious lesions where necessary in order to exclude diagnoses such epidermodysplasia verruciformis and verrucous carcinoma, which are HPV induced squamous cell carcinomas of the skin.[29]

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References

1. Clifton MM, Johnson SM, Roberson PK, et al. Immunotherapy for recalcitrant warts in children using intralesional mumps or Candida antigens. Pediatr Dermatol 2003;20:268–71.
2. Gibbs S, Harvey I. Topical treatments for cutaneous warts. Cochrane Database Syst Rev 2006;3:CD001781.
3. Sterling JC, Handfield-Jones S, Hudson PM. Guidelines for the management of cutaneous warts. Br J Dermatol 2001;144:4–11.
4. Handisurya A, Schellenbacher C, Kirnbauer R. Diseases caused by human papillomaviruses (HPV). J Dtsch Dermatol Ges 2009;7:453–66.
5. Jablonska S, Majewski S, Obalek S, et al. Cutaneous warts. Clin Dermatol 1997;15:309–19.
6. Gross G, Pfister H, Hagedorn M, et al. Correlation between human papillomavirus (HPV) type and histology of warts. J Invest Dermatol 1982;78:160–4.
7. Lipke MM. An armamentarium of wart treatments. Clin Med Res 2006;4:273–93.
8. Phoenix SL. Psychotherapeutic intervention for numerous and large viral warts with adjunctive hypnosis: a case study. Am J Clin Hypn 2007;49:211–8.
9. Dehghani F, Merat A, Panjehshahin MR, et al. Healing effect of garlic extract on warts and corns. Int J Dermatol 2005;44:612–5.
10. 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.
11. Stefani M, Bottino G, Fontenelle E, et al. Efficacy comparison between cimetidine and zinc sulphate in the treatment of multiple and recalcitrant warts. An Bras Dermatol 2009;84:23–9.
12. Tosti A, Piraccini BM. Warts of the nail unit: surgical and nonsurgical approaches. Dermatol Surg 2001;27:235–9.
13. Huo W, Gao XH, Sun XP, et al. Local hyperthermia at 44 degrees C for the treatment of plantar warts: a randomized, patient-blinded, placebo-controlled trial. J Infect Dis 2010;201:1169–72.
14. Sethuraman G, Richards KA, Hiremagalore RN, et al. Effectiveness of pulsed dye laser in the treatment of recalcitrant warts in children. Dermatol Surg 2010;36:58–65.
15. Togsverd-Bo K, Gluud C, Winkel P, et al. Paring and intense pulsed light versus paring alone for recalcitrant hand and foot warts: a randomized clinical trial with blinded outcome evaluation. Lasers Surg Med 2010;42:179–84.
16. Mitsuishi T, Wakabayashi T, Kawana S. Topical imiquimod associated to a reduction of heel hyperkeratosis for the treatment of recalcitrant mosaic plantar warts. Eur J Dermatol 2009;19:268–9.
17. Moore AY. Clinical applications for topical 5-fluorouracil in the treatment of dermatological disorders. J Dermatolog Treat 2009;20:328–35.
18. 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.
19. Dhar SB, Rashid MM, Islam A, et al. 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.
20. Summers P, Richards-Altmon P, Halder R. Treatment of recalcitrant verruca vulgaris with candida antigen in patient with human immunodeficiency virus. J Drugs Dermatol 2009;8:268–9.
21. Nofal A, Nofal E. Intralesional immunotherapy of common warts: successful treatment with mumps, measles and rubella vaccine. J Eur Acad Dermatol Venereol 2010 [Epub ahead of print].
22. Shivakumar V, Okade R, Rajkumar V. Autoimplantation therapy for multiple warts. Indian J Dermatol Venereol Leprol 2009;75:593–5.
23. Damstra RJ, van Vloten WA. Cryotherapy in the treatment of condylomata acuminata: a controlled study of 64 patients. J Dermatol Surg Oncol 1991;17:273–6.
24. 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.
25. Tobin AM, Cotter M, Irvine AD, et al. Successful treatment of a refractory verruca in a child with acute lymphoblastic leukaemia with topical cidofovir. Br J Dermatol 2005;152:386–8.
26. Sandoval M, Ortiz M, Diaz C, et al. Cutaneous manifestations in renal transplant recipients of Santiago, Chile. Transplant Proc 2009;41:3752–4.
27. Dharancy S, Catteau B, Mortier L, et al. Conversion to sirolimus: a useful strategy for recalcitrant cutaneous viral warts in liver transplant recipient. Liver Transpl 2006;12:1883–7.
28. Lowe S, Ferrand RA, Morris-Jones R, et al. Skin disease among human immunodeficiency virus-infected adolescents in Zimbabwe: a strong indicator of underlying HIV infection. Pediatr Infect Dis J 2010;29:346–51.
29. Dubina M, Goldenberg G. Viral-associated nonmelanoma skin cancers: a review. Am J Dermatopathol 2009;31:561–73.
30. Kalil CL, Salenave PR, Cignachi S. Hand warts successfully treated with topical 5-aminolevulinic acid and intense pulsed light. Eur J Dermatol 2008;18:207–8.

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