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# Recalcitrant nongenital warts

Nongenital warts are a common presentation in general practice. Despite treatment according to evidence based guidelines, a significant proportion of common warts fail to resolve, becoming recalcitrant. This poses a problem in clinical management. The recommendations for treating recalcitrant warts are unclear and there is a wide range of second line treatments available. This article reviews the available methods of treatment for recalcitrant nongenital warts as described in the medical literature.

**Keywords:** skin diseases



Nongenital warts affect 7–10%<sup>1</sup> of the general population and are a common dermatological condition in general practice. Human papilloma virus (HPV) is the causative agent, which enters via breaches in the skin surface and infects keratinocytes, resulting in metaplasia and excessive skin growth. There are multiple subtypes of HPV, depending on anatomical site and morphology. Subtypes 1, 2, 4, 27 and 57 lead to common warts on the hands and feet; whereas subtypes 3 and 10 give rise to planar warts on the hands and face.<sup>2</sup> Left alone, two-thirds of nongenital common warts will resolve spontaneously.<sup>3</sup> However, some do not resolve despite repeated treatment, these are referred to as 'recalcitrant warts'.

There is no exact definition for recalcitrance but a good rule to work by is 'failure to respond after five treatments over a period of 6 months'. Up to one-third of nongenital warts will become recalcitrant, especially the plantar, periungual and subungual types. Knowing that certain premalignant or malignant skin conditions can present as wart-like lesions (eg.

epidermodysplasia verruciformis and verrucous carcinoma), punch biopsy should be performed for histological diagnosis when in doubt. This article presents methods of treatment for recalcitrant nongenital warts.

## Topical applications

### 5-fluorouracil

An antineoplastic drug, 5-fluorouracil (5-FU) has been used as a topical agent in treating common warts<sup>3</sup> with cure rates in the range of 50–95%<sup>4,5</sup> when used alone compared to placebo. When combined with topical 10% salicylic acid, 5-FU improves cure rates of common warts by three times according to a German meta-analysis of randomised controlled trials.<sup>6</sup> The combination is considered a preferred treatment in recalcitrant common warts.<sup>7</sup> Recommended usage is 5% cream applied daily for up to 12 weeks with optional tape occlusion to enhance efficacy. Adverse effects include local irritation with erythema, scaling and cutaneous swelling, these effects are more pronounced when used on the face.<sup>8</sup> It can also lead to onycholysis when applied near the nail matrix.<sup>9</sup>

### 5% imiquimod cream

Imiquimod cream 5% is an immunomodulator which acts via the TLR-7 toll-like receptor found on the dendritic and Langerhans cells of the skin to enhance cell mediated immunity.<sup>10</sup> It was first approved and marketed for treating anogenital warts in 1997,<sup>11</sup> and its use has been currently extended to treat actinic keratosis and basal cell carcinoma.<sup>11,12</sup> For cutaneous recalcitrant warts, two open labelled trials using 5% topical imiquimod cream reported complete clearance in 80% of immunocompetent subjects<sup>13</sup> and observed benefits in 36% of immunosuppressed patients.<sup>14</sup> The recommended regimen is daily

application for 5 days per week for up to 16 weeks. Side effects include pain, pruritus and erythema, which are mild and well tolerated.<sup>13</sup>

## Intralesional injections

### Bleomycin sulphate

Bleomycin sulphate is a glycopeptide with antiviral, antibacterial and antineoplastic actions. Intralesional injection with bleomycin was first described for treating plantar warts in the 1970s<sup>15</sup> and various reports have described its use for recalcitrant warts with cure rates ranging from 14–99%.<sup>16</sup> Usual dosage per injection is 0.1–2.0 IU per lesion administered every 2 weeks. However, moderate to severe pain can develop due to the intralesional nature of injection and the compound itself. Remedies for this include modified delivery of bleomycin either with rapid lancet puncture<sup>17</sup> or the dermojet system, and mixing the bleomycin with local anaesthetics.<sup>18</sup>

Other complications include flagellate hyperpigmentation (a streaky pruritic urticarial skin eruption found over the upper trunk and limbs).<sup>19</sup> This occurs more often with bleomycin at systemic doses, however this has only been reported in a single case after intralesional injection.<sup>20</sup>

### Immunoreactive antigens

Intralesional injection of candida antigen for treating nongenital warts was first reported in 2001<sup>21</sup> and its indication has been highlighted for recalcitrant warts,<sup>22</sup> especially in children<sup>1</sup> and the immunosuppressed.<sup>23</sup> Adverse reactions include local pain and cyanosis when used to treat periungual wart.<sup>24</sup> Intralesional injection of mumps antigen has been used in a similar way for treating recalcitrant warts with comparable efficacy<sup>1,21,25</sup> which paved the way for the use of the measles, mumps and rubella (MMR) vaccine to treat resistant warts.<sup>26,27</sup> For best results with MMR vaccine, patients should undergo prior skin testing to confirm their responder status to MMR antigen<sup>21</sup> and to titrate the required dosage of vaccine injection.<sup>27</sup> Intralesional injection is repeated every 2–3 weeks for 3–5 consecutive treatments<sup>26,27</sup> or until resolution of the lesion. Response rates for recalcitrant warts has been quoted as high as 75–80%.<sup>26,27</sup>

## Physical destruction

Human papilloma virus enters epithelial cells and induces metaplasia of the keratinocytes which are shredded intact, hence the virions are rarely exposed to the immune active cells (ie. dendritic and Langerhans cells). They therefore succeed in evading clearance by the body's immune system and result in persistent infection. Any treatment that physically destroys the infected keratinocytes will have a chance of exposing the HPV virions, inducing cellular immunity and clearance. However, patients should be informed of potential scarring and that a previous history of keloid may indeed be a contraindication.

Three commonly used methods of physical destruction are described below.

### Liquid nitrogen

Liquid nitrogen boils at –196°C under normal atmospheric pressure and on contact with human skin induces rapid freezing of the tissue. As the nitrogen evaporates, the ice crystals in the skin thaw and disrupt the biomembranes of the epithelial cells. Repeated freeze-thaw cycles will kill and lyse the cells and release the HPV virions to be processed by the immune active cells. For recalcitrant cutaneous warts, the lesions are first pared down with a scalpel until capillary bleeding points are seen at the base before liquid nitrogen is applied. A longer contact time of 6 seconds (instead of the usual 3 seconds) is preferred for each freezing and four sets of freeze-thaw cycles are performed per treatment. This is repeated fortnightly.

### Hyfrecation

Hyfrecation is a form of high frequency electrosurgery where low power electrical impulses are delivered to the surface of the body via a pointed electrode.<sup>28</sup> Depending on how the electrode comes into contact with the skin surface, it results in either electrodesiccation (the tissue coagulates and desiccates without burning) or electrofulguration (resulting in burning and carbonisation of the tissue). Hyfrecation itself does not interfere with nerve conduction due to its high electrical frequency, yet it causes pain due to the generated heat and tissue burning. When used on recalcitrant warts, the lesions must be well anaesthetised with local anaesthetics (2% lignocaine or 0.5% marcaine)

to enable a good depth of tissue destruction. Again, the lesions should be pared down to the base before hyfrecation. The operator should be adept in switching between electrodesiccation and electrofulguration to achieve a fine control of the intended thickness of burning, especially in patients with anticipated poor wound healing due to diabetes or microvascular diseases. Hyfrecation is contraindicated in patients with a pacemaker due to potential interference from radiofrequency pulses generated by hyfrecation.

### Laser

Different types of lasers (carbon dioxide [CO<sub>2</sub>], KTP and pulse dye) have been described for treating recalcitrant warts<sup>29–33</sup> with a clearance rate up to 89% using pulse dye laser.<sup>31</sup> In essence, they all produce a controlled thermal destruction of the lesions with well defined skin radius and tissue depth as per the settings of the instrument. Traditional CO<sub>2</sub> lasers cause surgical destruction of the lesions with blistering, which is regarded as a hallmark of therapeutic efficacy.<sup>29</sup> When using the newer KTP laser and pulse dye laser, energy is selectively absorbed by the oxyhaemoglobin and dermal blood vessels without generalised tissue destruction occurs with the CO<sub>2</sub> laser. These laser treatments are generally well tolerated as pain is described as 'pinprick' and is comparable to that of cryotherapy.<sup>31,33</sup> No local anaesthesia is necessary. There is no burning of skin tissue or offensive smell as in hyfrecation, hence it is a preferable option for paediatric cases.<sup>30</sup> Special training is mandatory for laser operation and the instrument itself is often not an affordable purchase for the general practitioner.

### Surgery

Surgical removal is not an indicated treatment for recalcitrant cutaneous warts due to the high relapse rate and low cost effectiveness. However, surgical excision is indicated for recalcitrant conditions such as nonmalignant verrucous hyperplasia,<sup>34,35</sup> premalignant epidermodysplasia verruciformis,<sup>35</sup> and malignant verrucous carcinoma<sup>35,36</sup> after confirmation of histological diagnosis.

## Summary of important points

- Recalcitrant nongenital warts are defined as warts that failed five or more cycles of first

line treatment over a period of 6 months. They are not the same as recurrent warts which resolve then recur.

- One third of common warts become recalcitrant.
- Topical treatments such as 5% imiquimod or 5-FU cream should be tried before using intralesional injections or destructive treatments.
- For intralesional injections, bleomycin has the best evidence base compared to the newer immunoreactive antigens.
- For destructive treatments, aggressive cryotherapy and hyfrecation should be attempted first in the general practice setting before progressing to laser treatment.
- Combining treatments may have a higher chance of cure.
- If in doubt, perform biopsies to exclude premalignant or malignant lesions that can mimic the common wart.

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Conflict of interest: none declared.

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