Human papillomavirus infection

Treatment
Treatment depends on ........

| The wart       | size  |
|               | type  |
|               | number|
|               | site  |

| The patient   | expectations |
|               | circumstances|
|               | ability to self treat |

| The practitioner | expertise  |
|                 | time available |
|                 | treatments available |
Treatment options for genital warts

Topical applications
- podophyllotoxin
- imiquimod
- trichloracetic acid (TCAA)

Physical ablation
- cryotherapy
- electrosurgery
- excision
- laser
Treatment of genital warts

Lesion type

- Keratinised warts respond less well to podophyllotoxin or TCAA
- Non-keratinised warts usually respond well to podophyllotoxin
- Imiquimod and cryotherapy are suitable for both types
Treatment of genital warts

Lesion number
• Multiple warts
  • consider podophyllotoxin or imiquimod
  • cryotherapy useful but time consuming and limited by tolerability
  • consider excision if the warts are very large
• Few warts - consider cryotherapy, excision, TCAA

Lesion size
• Large warts – topical application but consider excision
• Small warts
  • any method may be suitable
  • consider number, type and site of warts
Treatment of genital warts

Lesion site – urethral meatus
- If warts fully visualised - consider cryotherapy, electrosurgery, podophyllotoxin or imiquimod
- Consider meatoscopy if upper limit cannot be visualised
  Intrameatal warts may be treated with cryotherapy or laser ablation via an auroscope ‘ear piece’
- Consider urology referral

Lesion site – anal canal
- Response to treatment may be slow
- Anoscopic examination via a proctoscope provides better visualisation
- Consider cryotherapy, TCAA, electrosurgery, laser ablation
Treatment of genital warts

Lesion site - cervix

- Consider colposcopy and biopsy prior to treatment
- Presence of CIN2/3 in addition to warts warrants LLETZ
- If only HPV/CIN1 on histology - consider cryotherapy, TCAA, laser ablation or loop excision (of warts only)
Treatment of warts in special groups

Pregnancy

- Reasons to consider treatment in pregnancy:
  - Minimise patient discomfort
  - Attempt to reduce neonatal exposure to virus
  - Risk of laryngeal papillomatosis (less than 1 in 1000)

- Reasons to defer/avoid treatment
  - Warts may regress spontaneously after delivery
  - More limited treatment options
  - Response to treatment may be poor

- Options
  - Cryotherapy
  - TCAA
  - Surgical excision

- Consider Caesarean section if large cervical or vaginal warts
  (very rarely required)
Treatment of warts in special groups

Immunosuppressed patients

- Warts more likely to be multiple and persistent
- Response to treatment often slow and relapse is common
- Treatment options – all treatment options as for immunocompetent patients are available
Treatment of warts in special groups

Children

- Multidisciplinary approach recommended
- Possibility of sexual abuse must be considered
- No treatment study data available
- Consider cryotherapy with EMLA (topical anaesthetic)
- Consider podophyllotoxin cream
- Or - consider awaiting spontaneous resolution
Podophyllin

• No longer recommended where podophyllotoxin available but mainstay of topical treatment for many years

• Crude resin extract from roots of the mayapple plant

• Non-standardised preparation containing multiple potentially active constituents, but the main active constituent is podophyllotoxin – a cytotoxic lignan

• Applied as 20 -25% solution in ethanol or tincture of benzoin

• Wash off 4-6 hours after application

• Repeat treatment 2-3 times per week
Podophyllin

Mechanism of action:

- Binds to intracellular microtubular proteins
- Leads to prevention of mitosis resulting in cell death

Side effects:

- Local inflammation, ulceration
- Systemic toxicity can occur after use of large volumes (e.g. vomiting, neuropathy, coma, pancytopaenia)
- Teratogenic
Podophyllotoxin

- Purified active ingredient of podophyllin
- Available as solution or cream
- Regimen - self-applied twice daily for 3 consecutive days - repeat weekly
- 0.15% cream and 0.5% solution are equally effective
- Local inflammation and ulceration may occur
- Not recommended in pregnancy
- Better clearance rates than podophyllin
Comparison of podophyllin vs podophyllotoxin in male patients with genital warts

RCT: 25% podophyllin vs 0.5% podophyllotoxin lotion

Proportion cleared at 5 weeks

<table>
<thead>
<tr>
<th></th>
<th>Podophyllotoxin</th>
<th>Podophyllin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prepuce</td>
<td>27/29 (93.1%)</td>
<td>12/13 (92.3%)</td>
</tr>
<tr>
<td>Glans</td>
<td>11/14 (78.6%)</td>
<td>5/7 (71.4%)</td>
</tr>
<tr>
<td>Shaft</td>
<td>16/21 (76.2%)</td>
<td>1/8 (12.5%)</td>
</tr>
<tr>
<td>Other</td>
<td>44/51 (86.3%)</td>
<td>13/21 (61.9%)</td>
</tr>
</tbody>
</table>
| All sites| 98/115 (85.2%)  | 31/49 (63.3%) p<0.002

(Kinghorn et al 1993)
Comparison of podophyllin vs podophyllotoxin in female patients with genital warts

RCT: 25% podophyllin vs 0.5% podophyllotoxin lotion

<table>
<thead>
<tr>
<th></th>
<th>Podophyllotoxin</th>
<th>Podophyllin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Labia majora</td>
<td>2/18 (66.7%)</td>
<td>5/11 (45.5%)</td>
</tr>
<tr>
<td>Labia minora</td>
<td>11/15 (73.3%)</td>
<td>5/8 (62.5%)</td>
</tr>
<tr>
<td>Introitus</td>
<td>10/14 (71.4%)</td>
<td>10/16 (62.5%)</td>
</tr>
<tr>
<td>Other</td>
<td>14/18 (77.8%)</td>
<td>7/11 (63.6%)</td>
</tr>
<tr>
<td>All sites:</td>
<td>47/65 (72.3%)</td>
<td>27/46 (58.7%) p=0.10</td>
</tr>
</tbody>
</table>

(Kinghorn et al 1993)
Trichloracetic Acid

• Caustic agent resulting in tissue necrosis

• Applied weekly in the clinic - with care – not suitable for self-treatment

• Not appropriate for ‘large volume’ warts
Cryotherapy

• Various devices:
  – Liquid nitrogen spray or probe
  – Nitrous oxide probe

• Causes:
  – intracellular ice formation leading to cell destruction
  – microvascular damage
  – secondary induction of a local immune response
Cryotherapy

- Used once weekly
- Freeze for 10-30 seconds post ‘ice ball’ formation
- Thaw and refreeze may improve response
- Erythema and ulceration may occur
- Safe in pregnancy
- Local anaesthesia rarely required
Electrocautery, scissor excision, laser ablation

- Single visit clearance takes time
- Tolerable with EMLA pre-injection of local anaesthetic
- Post treatment discomfort less with scissor excision
- Good smoke extraction system needed with laser
- Reported recurrence rates between 3% - 77%
## Cryotherapy vs TCAA
(Godley et al Genitourin Med 1987)

RCT: 130 men with penile warts; weekly treatment for 10 weeks;

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Cleared within 10 weeks</th>
<th>Mean no. of treatments</th>
<th>Recurrence at 2 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>TCAA</td>
<td>46 (81%)</td>
<td>4.0</td>
<td>14/39 (36%)</td>
</tr>
<tr>
<td>(n=57)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cryo</td>
<td>43 (88%)</td>
<td>3.0</td>
<td>15/38 (40%)</td>
</tr>
<tr>
<td>(n=49)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Podophyllin versus cryotherapy

*(Bashi Int J Derm 1985)*

<table>
<thead>
<tr>
<th>Treatment</th>
<th>No. treated</th>
<th>No. followed up</th>
<th>Cure rate at 6 weeks</th>
<th>Duration of treatment (weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>20% Pod (2x/week)</td>
<td>340</td>
<td>206</td>
<td>51%</td>
<td>4.7 +/- 2.4</td>
</tr>
<tr>
<td>Cryo (1x/week)</td>
<td>272</td>
<td>144</td>
<td>79%</td>
<td>2.3 +/- 1.2</td>
</tr>
</tbody>
</table>
Cryotherapy vs electrocautery  
(Simmons et al Br J Vener Dis 1981)

42 men with anogenital warts; treated for up to 3 months

<table>
<thead>
<tr>
<th></th>
<th>Number followed</th>
<th>Number cleared at 3 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cryotherapy</td>
<td>n=24</td>
<td>16</td>
</tr>
<tr>
<td>Electrocautery</td>
<td>n=18</td>
<td>11</td>
</tr>
</tbody>
</table>

p=NS
<table>
<thead>
<tr>
<th></th>
<th>Pod</th>
<th>Cryo</th>
<th>Electro</th>
<th>(All weekly)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. entered</td>
<td>144</td>
<td>154</td>
<td>152</td>
<td></td>
</tr>
<tr>
<td>No. completing treatment</td>
<td>63</td>
<td>68</td>
<td>88</td>
<td></td>
</tr>
<tr>
<td>Clear by 6 treatments</td>
<td>26</td>
<td>68</td>
<td>83</td>
<td>(41%) (79%) (94%)</td>
</tr>
<tr>
<td>Clear at 3-5 months</td>
<td>9/16</td>
<td>33/42</td>
<td>36/46</td>
<td>(56%) (79%) (78%)</td>
</tr>
</tbody>
</table>
Imiquimod

- Potent inducer of cytokines, particularly interferons via activation of monocytes/macrophages

- Increases local IFNα, IFNγ, TNFα, IL-12, which increases HPV specific CMI

- Apply as 5% cream thrice weekly

- Local reactions may occur

- Warts cleared in 50% patients by 16 weeks

- 10% recurrence of warts by 3 months

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## Use of imiquimod cream in anogenital warts

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Home based</td>
<td>Expensive</td>
</tr>
<tr>
<td>All external warts</td>
<td>Slow to act</td>
</tr>
<tr>
<td>Equal clearance to other topicals</td>
<td>Inflammation/irritation</td>
</tr>
<tr>
<td>Fewer relapses</td>
<td></td>
</tr>
</tbody>
</table>
Natural history of genital warts

- Spontaneous regression in 20-30% at 3 months
- Progression approximately 50% at 3 months
- Chronic persistence/recurrence 20%
Summary of published data on commonly used topical regimens for anogenital warts

<table>
<thead>
<tr>
<th>Treatment</th>
<th>End of treatment clearance (%)</th>
<th>Recurrence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Podophyllin*</td>
<td>32 - 79</td>
<td>11 - 65</td>
</tr>
<tr>
<td>Trichloroacetic Acid</td>
<td>50 - 81</td>
<td>36</td>
</tr>
<tr>
<td>Cryotherapy</td>
<td>63 - 88</td>
<td>0 - 39</td>
</tr>
<tr>
<td>Podophyllotoxin cream*</td>
<td>42 - 88</td>
<td>10 – 91</td>
</tr>
<tr>
<td>Imiquimod 5%</td>
<td>56 - 77</td>
<td>13 - 19</td>
</tr>
</tbody>
</table>

* Studies using more than one treatment strength grouped together

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# Home-based treatment for genital warts

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduce clinic visits</td>
<td>Lesion detection</td>
</tr>
<tr>
<td>Economical</td>
<td>Lack of monitoring</td>
</tr>
<tr>
<td>“Private”</td>
<td>Internal warts difficult</td>
</tr>
</tbody>
</table>

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