

National guideline for the management of anogenital warts

Clinical Effectiveness Group (Association for Genitourinary Medicine and the Medical Society for the Study of Venereal Diseases)

Aetiology

Anogenital warts are caused by the human papillomavirus (HPV) of which over 90 genotypes have been identified. The mode of transmission is most often by sexual contact but may be transmitted perinatally and from digital lesions usually in children. There is no good evidence of transmission from fomites. Most anogenital warts are benign and caused by types 6 and 11. Some lesions may contain oncogenic types associated with genital tract dysplasia and cancers. Anogenital warts are the 'tip of the iceberg' of genital infection with HPV, for example in the USA it has been estimated that there is an annual incidence of 1% of the adult population but many more people without warts have subclinical disease or latent infection⁽¹⁾.

Clinical features

Symptoms

In 1999 almost 65,000 new diagnoses of anogenital warts were made in England and Wales Genitourinary Medicine Clinics⁽²⁾. Although the large majority of these result in little physical discomfort, they are disfiguring and psychologically distressing⁽³⁾. They may cause irritation and soreness especially around the anus. Symptoms of distortion of urine flow or bleeding from the urethra, or anus, may indicate internal lesions.

Signs

Warts are benign epithelial skin tumours:

- HPV is a multifocal infection of the anogenital skin⁽⁴⁾ lesions being most common at the site of trauma at sexual intercourse, but may occur at any sites⁽⁵⁾.
- Perianal lesions are common in both sexes, but are seen more commonly in homosexual men⁽⁵⁾.
- Warts in the anal canal are associated with penetrative anal sex^(5,6), and may indicate the need for samples to be taken from the ano-rectal region for other STIs, e.g. N. Gonorrhoeae or C. Trachomatis.
- Occult lesions may be seen on the vagina, cervix, urethral meatus, and anal canal⁽⁵⁾.

- Extragenital lesions may be seen on the oral cavity, larynx, conjunctivae, and nasal cavity.

Clinical appearances of exophytic warts:

- Warts may be single or multiple.
- Those on the warm, moist, non-hair bearing skin tend to be soft and non-keratinised and those on the dry hairy skin firm and keratinised.
- Lesions may be broad based or pedunculated and some are pigmented.

Diagnosis

- Naked eye examination in most cases
- If in doubt, or lesion is atypical or pigmented, biopsy under local anaesthetic for histology should be performed prior to any therapeutic intervention. This may be aided by the use of a colposcope.

Assessment of lesions

- Examine the external anogenital and surrounding skin under good illumination
- Females, vaginal speculum
- Both sexes, proctoscopy may be indicated if history of anal receptive sex, or following clearance of perianal warts. Meatoscopy and proctoscopy should be performed if there is a history of distortion of urine flow or bleeding from the urethra or anus. Occasionally urethroscopy is indicated for more proximal warts.
- Classify warts as to morphology
- Recording of lesions on genital maps at each visit is useful, providing a visual record of approximate number, distribution, and response to treatment
- Extragenital sites (e.g. oral cavity) examined if clinically indicated.

Management

General advice

- Patients should be given a detailed explanation of their condition with particular emphasis on the long term implications for the health of themselves and their partners. This should be reinforced by giving them clear and accurate written information.

- Condom usage with regular sex partners has not been shown to affect the treatment outcome in anogenital warts⁽⁷⁾, although one study suggested a reduction in new HPV associated lesion formation⁽⁸⁾, but many patients and partners feel more comfortable using these while the warts are visible. The use of condoms may prevent transmission of HPV to uninfected partner(s)⁽⁸⁾ and should be encouraged.
- For some patients the psychological impact of warts is the worst aspect of the disease⁽²⁾. Where psychological distress is apparent, referral for counselling may be appropriate

Further investigations

Many patients will have other concurrent sexually transmitted infections (STI). Therefore, an appropriate screen for STI is recommended⁽⁹⁾.

Subclinical lesions

Subclinical lesions of the external anogenital skin are those not seen by the naked eye, but detectable by soaking the skin with 5% acetic acid and examining with a colposcope. These lesions are usually asymptomatic, but may cause irritation and inflammation of the skin- for example, atypical balanoposthitis⁽¹⁰⁾ or vulvitis⁽¹¹⁾.

Problems associated with the identification of such lesions :

- Many aceto-white lesions are not caused by HPV⁽¹²⁾
- Histological changes are not specific for HPV infection⁽¹³⁾
- HPV identification is not routinely available.

Treatment of these has not been shown to:

- affect the course of disease⁽¹⁴⁾
- affect the course of disease in partners⁽⁷⁾

For the above reasons and the fact that identification may cause unnecessary distress, it is not recommended that these lesions are sought unless there is a clinical indication (level of evidence IIb, grade of recommendation B)

Treatment

- All treatments have significant failure and relapse rates.
- Treatment decisions should be made after discussing the appropriate options with the patient, taking into account their preference and convenience.
- Treatment may involve discomfort and local skin reactions. Written information on management of treatment side effects is recommended.
- Local anaesthetic creams plus or minus injection with e.g. Lignocaine 2% could be used before ablative therapy to minimise discomfort. Adrenaline-containing anaesthetic should be avoided for lesions on the penis and around the clitoris.
- Warticon and Condylone (Podophyllotoxin) hold license for treatment of genital warts but not extragenital lesions such as anal warts. They are licensed for 4 and 5 week courses respectively. It is recommended that when lesion area treated is greater than 4 cm² that treatment takes place under direct supervision of medical staff. 5-Fluorouracil is licensed for treatment of malignant and non-malignant skin lesions. Common practice in the treatment of anogenital warts is to use these compounds out of license. It should be noted that such use is a doctor's responsibility.
- Treatment choice
- The evidence base to direct first and second line treatments is not strong.
- Treatment choice depends on the morphology, number, and distribution of warts.
- Soft non-keratinised warts respond well to podophyllin, podophyllotoxin, and trichloroacetic acid.
- Keratinised lesions are better treated with physical ablative methods such as cryotherapy, excision, or electrocautery⁽¹⁵⁾
- Imiquimod may be suitable for both types.
- People with a small number of low volume warts irrespective of type are best treated with ablative therapy from the outset.
- Podophyllotoxin, for 4 week cycles and imiquimod for up to 16 weeks are suitable for home treatment by patients. If chosen, the patient should be given a demonstration on lesion finding and treatment application.
- No treatment is an option at any site and may apply particularly to warts in the vaginal and anal canal.

- Treatments available

Clearance and recurrence rates for individual treatments are shown in table 1⁽¹⁶⁾.

Table 1 Overview of clearance and recurrence rates in the published literature with different treatments for external genital warts

Treatment	Clearance rates (%)		Recurrence rates (%)
	End of treatment	≥ 3 months	
Cryotherapy	63-88	63-92	0-39
Electrocautery/electrotherapy	93-94	78-91	24
Interferon			
Intralesional	19-62	36-62	0-33
Systemic	7-51	18-21	0-23
Topical	6-90	33	6
Laser therapy	27-89	39-86	<7-45
LEEP	< 90	-	-
Podophyllin	32-79	22-73	11-65
Podophyllotoxin	42-88	34-77	10-91
Imiquimod	50-62	50-62	13-19
Surgical/scissor excision	89-93	36	0-29
TCA	50-81	70	36

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When interpreting this table it is important to take into account that studies are not strictly comparable as methods and endpoints differ across the studies.

Chemical applications

Podophyllin

Podophyllin is a non-standardised cytotoxic compound. It has been associated with severe local reactions. Serious systemic adverse events have occurred when used outside guidelines⁽¹⁷⁾. Podophyllin is licensed for prescription use only. Best practice described in the British National Formulary recommends supervised application in GUM clinics or general practice by trained nurses after screening for other STDs. Animal experiments indicate teratogenic and oncogenic properties⁽¹⁸⁻²²⁾ but evidence of these in humans is lacking

- 15-25% solution can be carefully applied to lesions, in clinic, once or twice weekly. Wash off 4 hours later (Ib,A)
- Approximate cost £3.00/10 ml.

Caution:

- Podophyllin has caused serious systemic side effects if applied in excess. Increased systemic absorption is likely if used internally. Limit application to 10 cm² or 0.5 ml for external warts, and less than 2 cm² for vaginal warts (IV,C) ⁽²³⁾.
- The potential oncogenic and teratogenic effects as noted indicate it should be avoided on the cervix and in the anal canal, and in pregnancy (IV/C).

The adverse problems associated with Podophyllin and its inferior efficacy to Podophyllotoxin⁽²⁴⁻²⁷⁾ (IIaB) - greater than 20% clearance in each of the quoted studies in favour of Podophyllotoxin - have led some experts to no longer recommend the use of Podophyllin⁽²⁸⁾.

Combination therapy

Applying Podophyllin in conjunction with cryotherapy is a common practice in the UK ⁽²⁹⁾ although there are no studies to validate this approach.

Podophyllotoxin

Podophyllotoxin, a purified extract of podophyllin in the form of a 0.5% solution or 0.15% cream, is suitable for home treatment (Ib, A).

- Treatment cycles consist of twice daily application for 3 days, followed by 4 days' rest for 4 cycles.
- The cream may be easier for many patients to apply, especially at the anus.
- Discontinue treatment if significant side effects.
- Cost: 0.5% solution 3 ml to £14.50, 0.15% cream 5 g, £17.40.

Caution: Avoid in pregnancy.

Trichloroacetic acid

Trichloroacetic acid (TCA) 80-90% solution is suitable for weekly application in a specialist clinic setting only. It acts as a caustic agent resulting in cellular necrosis) (Ib, A).

- An intense burning sensation may be experienced for 5-10 minutes after application.

- Ulceration penetrating into the dermis may occur, and it is therefore not recommended for large volume warts.
- TCA can be used at most anatomical sites.
- Approximate cost: 10 ml, £3.00.

Caution

- TCA is extremely corrosive to the skin. Careful application and protection of the surrounding skin with petroleum jelly is recommended. A neutralising agent-for example, sodium bicarbonate, should always be available in case of excess application or spills.

5-Fluorouracil

5-Fluorouracil is a DNA antimetabolite, available in a 5% cream. Its use is limited by severe local side effects, which may result in long term problems- for example, neovascularisation and vulval burning. It may be teratogenic, therefore should not be used in pregnancy. It is not commonly used and as satisfactory alternatives exist, this treatment is no longer recommended unless with expert advice

Interferons

Various regimens have been described using interferons alfa, beta, and gamma as creams and as intralesional or systemic injection (Ib, A).

- Its use is limited by expense, systemic side effects, and a variable response rate.
- Cyclical low dose injection used as an adjunct to laser therapy has resulted in a lower relapse rate⁽³⁰⁾.
- Interferons should only be used on consultant advice.

Imiquimod

Imiquimod is an immune response modifier.

- Available as a 5% cream, it induces a cytokine response when applied to skin infected with HPV⁽³¹⁾.
- Suitable for use on all external AGW but is not recommended for use in pregnancy or internally.
- Use in uncircumcised men has been shown to be safe⁽³²⁾.

- Cream is applied to lesions three times weekly and washed off 6-10 hours later for up to 16 weeks.
- Response to treatment may be delayed for some weeks.
- Clinical trials have shown response rates comparable with other chemical agents, but an apparently low relapse rate (Ib, A) ^(33,34). An apparently low relapse rate has not been compared in clinical trials against other currently available therapies.
- Cost: £55.18 for 4 week course.

Caution: Not approved for use in pregnancy or internally.

Physical ablation

Excision (Ib, A)

- Removal of warts under local anaesthetic injection is particularly useful for pedunculated warts, and small numbers of keratinised ones at anatomically accessible sites.
- Haemostasis can be established using electrosurgery or application of a haemostatic solution.
- Treatment can be repeated as required. This is a good method of treatment for small numbers of warts and may be underused⁽³⁵⁾

Cryotherapy (Ib, A)

- Using a liquid nitrogen spray or a cryoprobe causes cytolysis at the dermal epidermal junction resulting in necrosis.
- Treatment should be applied until a "halo" of freezing has been established a few millimetres round the treated lesion.
- A freeze, thaw, freeze technique should be used
- Cost of liquid nitrogen spray £575.00 + VAT

Electrosurgery (Ib, A)

Three types are commonly used:

- Electrocautery results in burning of the treatment site and surrounding tissue. Cost £490.83 + heads £15.00-£59.95

- Hyfrecator acts by electrofulguration resulting in superficial charring and little dermal damage, or for deeper tissue penetration electro desiccation. These can be followed by curettage. Cost: £935.50 + VAT.
- Monopolar surgery- different waveforms can be generated, allowing desiccation, cutting, or coagulation. This results in a cleaner cut and less damage to surrounding tissue⁽³⁶⁾. Cost, £1,995.00 + VAT. Heads £12.95 + VAT

Caution: leave skin bridges between treatment sites to aid healing and minimise scarring.

Laser treatment (IIa, B)

- The carbon dioxide laser is especially suitable for large volume warts and can be used at difficult anatomical sites, such as the urethral meatus, or intra-anal⁽³⁷⁾.

Cost : £30 000 + VAT.

Caution:

All electrosurgical and laser techniques result in a plume of smoke which has been shown to contain HPV DNA, which may potentially cause infection of the respiratory tract in operating personnel. Therefore, masks should be worn and adequate extraction provided during these procedures (IIb, B)⁽³⁸⁾.

Costs for all of the above are approximate as at time of submission.

Sexual partners

- Current sexual partner(s) may benefit from assessment as they may have undetected genital warts, undetected other STI, or need an explanation and advice about disease process in partner (III, B).
- Tracing of previous sexual partner(s) is not recommended.

Follow up

- Review at end of course to monitor response and assess need for changes in therapy. Patients whose original lesions have responded well to treatment but new lesions are evolving, can continue with current regimen.
- Change is indicated if (a) patient is not tolerating current treatment, (b) under 50% response to current treatment.
- Relapses should be treated as appropriate to the lesion types.

Special considerations

Anatomical sites

Podophyllin and 5 Fluorouracil are no longer recommended for internal lesions

Intravaginal

- Cryotherapy, electrosurgery and trichloroacetic acid are recommended treatments.
- If Podophyllin is used it should be applied carefully to no more than a total area of 2 cm² weekly.

Cervix

- Best practice suggests colposcopy and biopsy before treatment decisions⁽³⁹⁾
- If no CIN, cryotherapy, electrosurgery or trichloroacetic acid may be used. If CIN, refer for large loop excision of the transformation zone (LLETZ).

Urethral meatus

- If base of lesions seen, treatment with cryotherapy, electrosurgery, podophyllotoxin or imiquimod. Lesions deeper in the urethra should be referred to Urology for surgical ablation under direct vision.

Intra-anal

- Treatment options include trichloroacetic acid, cryotherapy, electrosurgery, and laser treatment.

Pregnancy

- Avoid podophyllin, podophyllotoxin, and 5-fluorouracil because of possible teratogenic effects.
- Imiquimod is not approved for use in pregnancy. If using after informed consent, treatment should be registered with 3M monitoring system

Contact Details:

Pharmacovigilance Unit, 3M Health Care Limited, 3M House, Morley Street, Loughborough, Leicestershire, LE11 1EP)

- Treatment aims to minimise the number of lesions present at delivery to reduce the neonatal exposure to virus.
- Potential problems for children are the development of laryngeal papillomatosis⁽⁴⁰⁾ and anogenital warts⁽⁴¹⁾

- Very rarely a caesarean section is indicated because of blockage of the vaginal outlet with warts or the presence of gross cervical warts.

Cervical cytology

- The National Health Service Cervical Screening Programme recommends that no changes are required to screening intervals in women with anogenital warts
- Guidelines for the management of abnormal smears have been defined⁽⁴²⁾.

Immunosuppressed

- People with impaired cell mediated immunity- for example, renal transplant patients or HIV infection, are likely to have poor treatment responses, increased relapse rates, and dysplasia.
- Careful follow up is required in all these patients.

Auditable outcome measures

- The use of a treatment protocol has been shown to improve the management of genital warts⁽⁴³⁾ It is recommended that a continuing audit cycle is adopted to ensure effective use of a protocol and for the incorporation of any new treatments available.
- Recommended outcomes are:
- Adherence to protocol, 90% of patients
- Percentage of patients with wart clearance at 3 months
- Percentage of patients with recurrence within 6 months of initial clearance.

Author and centre

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Membership of the CEG

Clinical Effectiveness Group: chairman, Keith Radcliffe (MSSVD); Imtyaz Ahmed-Jushuf (AGUM); Jan Welch (MSSVD); Mark FitzGerald (AGUM); Janet Wilson (Royal College of Physicians GU Medicine Committee).

Potential conflicts of interest

Dr Birley has chaired a sponsored meeting for 3M, Dr Jenkins has acted as a consultant to Merck and 3M, Dr Maw has acted as a consultant to 3M, Perstorp and Stiefel, Dr Ross is in receipt of research grants from 3M and Stiefel, Dr Sonnex has conducted clinical trials for 3M and Stiefel

Evidence base

OVID/Medline was searched for the years 1966-2000 using keywords "human papillomavirus," "genital warts," "epidemiology," "clinical manifestations," "treatment," "management," "laryngeal papillomatosis."

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