Warts - anogenital - Management

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How do I make a diagnosis of anogenital warts?

- Diagnosis is made by examination with the naked eye in most cases [BASHH, 2007]:

  - Lesions may be single or multiple and tend to occur in areas that are traumatized during sexual intercourse [von Krogh et al, 2000].

  - Warts on dry, hairy skin tend to be firm and keratinized (horny). Those on warm, moist, non–hair-bearing skin tend to be soft and non-keratinized. Lesions may be broad-based or pedunculated (attached by a stalk), and some are pigmented [BASHH, 2007].

How should I assess a person with anogenital warts?

- Take a brief sexual history to establish the risk of co-existing sexually transmitted infection:

  - In men, ask about the presence of urethral discharge and dysuria.

  - In women, ask about vaginal discharge and intermenstrual or post-coital bleeding.

  - Ask about current and previous partners.

  - Ask about the use of barrier contraception.

- Ask about distortion of urine flow or bleeding from the urethra (suggesting an intrameatal wart) and bleeding from the anus.

- Consider the possibility of pregnancy, HIV, or immunosuppression.

- Inspect the external genitalia and perianal area to confirm the diagnosis and establish the extent of lesions (see www.chestersexualhealth.co.uk for photos).

- Consider other possible diagnoses: see Additional information.

Additional information

- The most common lesions misdiagnosed as anogenital warts are:

  - In men, 'pearly penile papules': 1–3 rows of physiological, smooth, discrete, non-coalescing, 1–2 mm papules appearing on the margin of the glans (see www.chestersexualhealth.co.uk for a photo).

  - In women, 'micropapillomatosis labialis': physiological, regularly shaped and non-coalescing, mostly symmetrical papillae appearing on the inner surface of the labia minora and vestibule.

- Other common, benign differential diagnoses are molluscum contagiosum, skin tags, seborrhoeic keratoses, and sebaceous glands of the foreskin and vulva.

- Consider vulval, penile, or anal intraepithelial neoplasia if the lesions are flat, only slightly raised, or pigmented.

- Consider other possible sexually transmitted infections such as secondary syphilis, which may present as anogenital condylomata lata (moist warty lesions at sites of skin friction such as perianal and vulval areas).

- Consider frank malignancy if the lesions are ulcerated or bleeding.

Basis for recommendation

- These recommendations are based on the British Association for Sexual Health and HIV (BASHH) *United Kingdom national guideline on the management of anogenital warts* [BASHH, 2007], joint recommendations on *Sexually transmitted infections in primary care* [RCGP and BASHH, 2006], European *Guidelines for primary care physicians for the diagnosis and management of anogenital warts* [von Krogh et al, 2000], and a review [Lacey, 2000].

  - Whilst obtaining a sexual history is generally recommended, UK primary care guidelines acknowledge that it may be appropriate to leave a detailed sexual history to the genito-urinary medicine clinic [RCGP and BASHH, 2006].

  - Although none of the guidelines make specific recommendations on history-taking, BASHH states that a history of distortion of urine flow, or

bleeding from the urethra or anus, may indicate internal lesions [BASHH, 2007]. This is important because European guidelines recommend that people with internal lesions, as well as pregnant women and people with immunosuppression, should be assessed and treated in secondary care [von Krogh et al, 2000].

o Differential diagnoses and features of malignancy and intraepithelial neoplasia are derived from European guidelines, a review article, and joint recommendations on *Sexually transmitted infections in primary care* [Lacey, 2000; von Krogh et al, 2000; RCGP and BASHH, 2006].

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Who should I refer?

- Referral to a sexual health specialist is recommended for all people with anogenital warts.
- Referral is essential in the following situations:

o Uncertain diagnosis.

o Suspected malignancy or intraepithelial neoplasia.

o Immunosuppression, including HIV.

o Present or suspected cervical, intrameatal, or intra-anal warts.

o Pregnancy.

o Children.

- Consider the possibility of sexual abuse in any child with anogenital warts, particularly if younger than 13 years of age. Follow appropriate child protection procedures and refer to a paediatrician if necessary.
- Only offer treatment for anogenital warts in primary care (see Management) if:

- Referral to a sexual health specialist is not possible (because it is declined or unavailable) and you are confident of the diagnosis of external genital warts, *or*

- You have the skills and resources to provide comprehensive assessment and treatment, as well as screening and contact tracing for other sexually transmitted infections.

- Consider referral for counselling if the person has psychological distress.

Additional information

Treatments recommended for use in secondary care include [BASHH, 2007]:

- Podophyllotoxin.

- Cryotherapy.

- Imiquimod.

- Electrosurgery.

- Trichloroacetic acid.

- Excision.

- Laser treatment.

- Surgical ablation of intrameatal warts (in urology or genito-urinary medicine).

Basis for recommendation

- **Referral to a sexual health specialist is recommended for all people with anogenital warts:** neither of the UK guidelines had explicit recommendations regarding routine referral [RCGP and BASHH, 2006; BASHH, 2007], and CKS could find no studies comparing primary and secondary care management. Although European [von Krogh et al, 2000] and US [ACOG, 2005] guidelines state that non-specialists can deal with the majority of anogenital warts, there are

convincing arguments in favour of referral of all people with anogenital warts. These arguments are discussed in a round table meeting report [Succinct Communications Limited, 2001]:

- Sexual health specialists have the expertise and resources to:

- Provide more effective screening for co-existing sexually transmitted infections (STIs), which will require treatment and contact tracing [RCGP and BASHH, 2006].

- Ensure accurate and complete diagnosis: anogenital warts are commonly missed or misdiagnosed unless the person is assessed by someone experienced in examining the anogenital region [Succinct Communications Limited, 2001].

- Offer a comprehensive range of treatments: see Additional information.

- Ensure that consistent information is conveyed to the person and follow up provided to allow early switching if first-line treatments are ineffective [Succinct Communications Limited, 2001].

- Some people will value the additional confidentiality provided by genito-urinary medicine clinics [Succinct Communications Limited, 2001].

▪ **Referral is essential in the following situations:** these recommendations are based on the British Association for Sexual Health (BASHH) and HIV *United Kingdom national guideline on the management of anogenital warts* [BASHH, 2007], joint recommendations on *Sexually transmitted infections in primary care* [RCGP and BASHH, 2006], and European *Guidelines for primary care physicians for the diagnosis and management of anogenital warts* [von Krogh et al, 2000]:

- **Uncertain diagnosis or possible malignancy:** BASHH recommends biopsy 'if in doubt, or if the lesion is atypical or pigmented' [BASHH, 2007].

- **People with immunosuppression** are likely to have poor treatment responses, increased relapse rates, and an increased risk of developing anogenital intraepithelial neoplasia [BASHH, 2007].

- **Cervical warts:** referral for colposcopy is recommended in older UK and European primary care guidelines [von Krogh et al, 2000; RCGP and BASHH, 2006], but more recent BASHH guidelines do not recommend colposcopy in

women with genital warts, unless 'there was diagnostic uncertainty or clinical concern' [BASHH, 2007]. CKS suspect that most GPs will not be sufficiently confident to differentiate a cervical wart from a more serious cervical lesion, and so the decision regarding colposcopy should lie with the sexual health specialist.

- **Anal and suspected intra-anal warts:** referral is recommended in European guidelines [von Krogh et al, 2000]. BASHH recommends proctoscopy in individuals with a history of receptive anal sex [BASHH, 2007]. Referral is generally required, as there is rarely the expertise in primary care to perform this procedure.

- **Intrameatal warts:** referral is recommended in UK and European guidelines [von Krogh et al, 2000; RCGP and BASHH, 2006].

- **Pregnancy:** referral for treatment is recommended in European guidelines [von Krogh et al, 2000]. Treatment aims to minimize the number of lesions present at delivery to reduce the neonatal exposure to virus, as neonates are at risk of laryngeal papillomatosis and anogenital warts [BASHH, 2007]. A further reason for referral is that self-applied treatments are contraindicated in pregnancy [BASHH, 2007], and ablative methods will therefore be needed if treatment is indicated.

- **Children:** the recommendation to refer children is based on European guidelines [von Krogh et al, 2000] and the British National Formulary for Children, which states that imiquimod and podophyllotoxin are not licensed in children and that treatment should be supervised by a hospital specialist [BNF for Children, 2007].

- **Consider the possibility of sexual abuse in any child with anogenital warts:**

  - This advice is based on European guidelines [von Krogh et al, 2000] and usual child protection procedures. Whilst anogenital warts in pre-pubertal children may be associated with sexual abuse [Ingram et al, 1992; Moscicki, 1996], there are no recent studies that relate specifically to adolescents (13 years of age or older, corresponding to the scope of this topic). As with any STI in an adolescent, clinical judgement should be used to determine whether anogenital warts may be the result of sexual abuse.

- **Only offering treatment for anogenital warts in primary care:** these recommendations are based on joint Royal College of General Practitioners/BASHH recommendations [RCGP and BASHH, 2006] and on the *National strategy for sexual health and HIV* [DH, 2001], the latter stating that 'GPs and nurses with a special interest in providing (sexual health) services will need to undertake specific training to develop and maintain the skills required'.

- **Consider referral for counselling if the person has psychological distress:** this is based on UK guidelines [BASHH, 2007].

How should I manage a person with anogenital warts in primary care if referral is not possible?

- Screening for co-existing sexually transmitted infections (STIs) is essential, particularly in people younger than 25 years of age and those with other genital symptoms.

- Do a vaginal speculum examination in women.

- Do a proctoscopy (where available) if there is a history of anal receptive sex.

- Tracing of previous sexual partner(s) is not recommended for people with anogenital warts in the absence of other STIs.

- Because evidence comparing efficacy is insufficient, choice of treatment should depend on the person's preference; number, volume, type and site of lesions; availability; and cost.

- Inform that active treatments:

  - Have significant failure rates.

  - Have significant relapse rates (because they do not eliminate the human papillomavirus).

  - Often involve discomfort and skin reactions.

- Treatment options include:

  - **No treatment:** as one-third of visible warts disappear spontaneously within 6 months, no treatment is an option for anogenital warts at any site.

  - **Self-applied treatments** cannot be used in pregnancy, are not licensed for use in children, and have a high likelihood of adverse effects. If a self-

applied treatment is chosen, show the person the location of the warts and where to apply topical treatment (to reduce treatment failure owing to undertreatment):

- **Podophyllotoxin** 0.5% solution or 0.15% cream (Condyline® or Warticon®) is useful for soft, non-keratinized (non-horny), external lesions but is not licensed for anal warts; cream may be easier to apply. Supervision by a healthcare professional is recommended when the lesion area to be treated is greater than 4 cm^2 — see Advice and Prescriptions.

- **Imiquimod** 5% cream (Aldara®) may be suitable for both keratinized (horny) *and* non-keratinized, external genital, and perianal warts but is not recommended for internal use — see Advice and Prescriptions.

- **Ablative methods** (such as cryotherapy, excision, and electrocautery): consider if appropriately trained and resourced. Cryotherapy is recommended in people with a small number of low-volume warts (regardless of type) and is useful for keratinized warts.

- Follow up to assess response and whether treatment is tolerated, and to look for new lesions:

  - Continue treatment if the original lesions respond well to treatment but new lesions are developing.

  - Change treatment if it is not tolerated or response to treatment by 6 weeks (8–12 weeks for imiquimod) is inadequate.

Additional information

- Imiquimod currently costs £51.32 for 28 days' treatment compared with £12.88 to £15.46 for podophyllotoxin [BNF 55, 2008].

- The following treatments are not recommended because of high rates of adverse effects and the presence of alternative, effective treatments [BASHH, 2007]:

  - Podophyllin.

  - 5-fluorouracil.

  - Topical interferon.

Basis for recommendation

- These recommendations are based on UK [BASHH, 2007], UK primary care [RCGP and BASHH, 2006], European primary care [von Krogh et al, 2000] and US [CDC, 2006; ACOG, 2007] guidelines, as well as one evidence-based review [Buck, 2007], three systematic reviews [Moore et al, 2001; Yan et al, 2006; Jaffary et al, 2007], and one observational study [Griffiths et al, 2006]:

  - All of the guidelines recommend screening for co-existing sexually transmitted infections (STIs) because of the high prevalence in people with anogenital warts. A retrospective, observational study found (using logistic regression) that age younger than 25 years and other genital symptoms were each associated with a statistically significant increased odds of co-existing STI compared with age older than 25 years and no genital symptoms [Griffiths et al, 2006]. However, the authors appear not to have adjusted for any factors other than gender, which raises the possibility of confounding or effect modification.

  - The recommendations regarding vaginal speculum examination and proctoscopy, previous partner tracing, choice of treatment, treatment advice, and follow up are based on UK and US guidelines [ACOG, 2005; CDC, 2006; BASHH, 2007].

  - **No treatment** is an option, as anogenital warts are usually benign and one-third of visible warts disappear spontaneously within 6 months [RCGP and BASHH, 2006; BASHH, 2007].

  - **Imiquimod:** evidence from three systematic reviews, two of which included meta-analyses (three RCTs, n = 358; four RCTs, n = 528), suggests that imiquimod is superior to placebo but is associated with a high rate of adverse effects.

  - **Podophyllotoxin:** evidence from one systematic review (nine RCTs; n = 479 using podophyllotoxin and 294 using placebo) suggests that podophyllotoxin is superior to placebo but is associated with a high rate of adverse effects.

- CKS found no studies comparing imiquimod with podophyllotoxin.

- **Ablative methods** (cryotherapy, surgical excision, and electrosurgery) are likely to be beneficial [Buck, 2007]. Cryotherapy is recommended in people with a small number of low-volume warts (regardless of type) [BASHH, 2007] and as a treatment option if referral to genito-urinary medicine is not possible [RCGP and BASHH, 2006]. It is useful for keratinized warts [RCGP and BASHH, 2006; BASHH, 2007]. CKS found no studies comparing cryotherapy with no active treatments; the recommendation for cryotherapy as a treatment option is based on clinical consensus [von Krogh et al, 2000; Buck, 2007]. Cryotherapy has not been directly compared with imiquimod or podophyllotoxin, but it appears to be as effective as trichloroacetic acid (secondary care treatment only) and electrosurgery [Buck, 2007].

What advice should I give to a person with anogenital warts?

- Explain the person's condition and treatment, providing clear and accurate written information.

- Advise women that no changes are recommended in the screening intervals of cervical cytology.

- Advise condom use and smoking cessation to improve response to treatment.

- If asked, reassure that the presence of anogenital warts does not always imply recent partner infidelity because human papillomavirus is thought to have a long latency period.

- Suggest that, with consent, the person's current sexual partner may benefit from assessment for undetected genital warts or other undetected sexually transmitted infections, or for explanation and advice about the disease process in their partner.

- Advise anyone using imiquimod:

  - To avoid normal or broken skin and open wounds.

  - To avoid unprotected sexual contact soon after application because of a possible irritant effect on the partner.

  - That latex condoms may be weakened if in contact with imiquimod.

- That response to treatment and adverse effects may be delayed by some weeks.

- That inflammation may occur within a few applications of imiquimod (because the immune system has been stimulated rapidly). If this happens, stop applying the cream, allow the redness to subside, and then gradually reintroduce it twice or even once a week.

- That permanent hypopigmentation and hyperpigmentation may occur.

▪ Advise anyone using podophyllotoxin:

- To avoid normal skin and open wounds.

- To avoid unprotected sexual contact soon after application because of a possible irritant effect on the partner.

- That podophyllotoxin can cause local irritation of the treated area. This may occur on the second or third day of application and decreases after treatment is discontinued. In most cases, the reactions are mild.

- To discontinue treatment if there are significant adverse effects, such as soreness or ulceration.

- To not apply excessive amounts and follow the instructions for application carefully. Excessive application may cause severe systemic toxicity, including gastrointestinal, renal, haematological, and central nervous system effects.

▪ For more detailed information on using imiquimod and podophyllotoxin, see individual Summaries of Product Characteristics and patient information leaflets at http://emc.medicines.org.uk.

Basis for recommendation

▪ Recommendations regarding explanation, provision of written information, cervical cytology, and assessment of current sexual partner are based on the *United Kingdom national guideline on the management of anogenital warts* [BASHH, 2007].

▪ The recommendation on condom use is based on the *United Kingdom national guideline on the management of anogenital warts*, which states, 'Although data are conflicting, condoms have

been shown to protect against the acquisition of HPV (human papillomavirus) infection and genital warts and may also have a therapeutic effect when both partners are infected' [BASHH, 2007].

- The recommendation to advise smoking cessation is based on data in the *United Kingdom national guideline on the management of anogenital warts*, which suggests that smokers respond less well to treatment than non-smokers [BASHH, 2007].

- The recommendation to reassure, if asked, that the presence of anogenital warts does not always imply recent partner infidelity is from joint recommendations on *Sexually transmitted infections in primary care* [RCGP and BASHH, 2006] and the European *Guidelines for primary care physicians for the diagnosis and management of anogenital warts* [von Krogh et al, 2000].

- Advice for anyone using imiquimod and podophyllotoxin is from the *United Kingdom national guideline on the management of anogenital warts* [BASHH, 2007], the British National Formulary [BNF 55, 2008], and an expert reviewer.

Prescriptions

For information on contraindications, cautions, drug interactions, and adverse effects, see the electronic Medicines Compendium (eMC) (http://emc.medicines.org.uk), or the British National Formulary (BNF) (www.bnf.org).

Podophyllotoxin

Age from 18 years onwards

Podophyllotoxin 0.15% cream (4 week treatment)

Warticon 0.15% cream
Apply twice a day for 3 consecutive days. Repeat at weekly intervals if necessary for a maximum of four 3-day treatment courses.
Supply 5 grams.

Age: from 18 years onwards
NHS cost: £15.46
Licensed use: yes

Patient information: Before applying the cream wash the affected area thoroughly with soap and water, and dry. Using a fingertip, apply the cream, using only enough cream to just cover each wart. Wash your hands after you apply the cream.

Podophyllotoxin 0.5% solution (4 week treatment)

Warticon 0.5% solution
Apply twice a day for 3 consecutive days using the applicator provided. Repeat at weekly intervals as necessary for a maximum of four 3-day treatment courses.
Supply 3 ml.

Age: from 18 years onwards
NHS cost: £12.88
Licensed use: yes

Patient information: Wash your hands after each application.

Podophyllotoxin 0.5% solution (5 week treatment)

Condyline 0.5% solution
Apply twice a day for 3 consecutive days using the applicator provided. Repeat at weekly intervals if necessary for a maximum of five 3-day treatment courses.
Supply 4 ml.

Age: from 18 years onwards
NHS cost: £14.49
Licensed use: yes

Patient information: Wash your hands after each application.

Imiquimod

Age from 18 years onwards

Imiquimod 5% cream (up to 16 weeks treatment)

Imiquimod 5% cream 250mg sachets
Apply thinly three times a week (e.g. Monday, Wednesday, and Friday) at bedtime until lesions resolve for a maximum of 16 weeks.
Supply 12 sachets.

Age: from 18 years onwards
NHS cost: £51.42
Licensed use: yes

Patient information: Rub the cream into the affected area, wash you hands after application. Allow the cream to stay on the affected area for 6-10 hours, then washed off with a mild soap and water. Avoid unprotected sex soon after application because of a possible irritant effect on the partner.