Section A -Research paper

Anogenital Warts

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Abstract:

Anogenital warts (AGWs) rank among the most frequent sexually transmitted infections in young adults. They are benign lesions, but they pose a significant economic cost to health care systems and a substantial psychological burden on patients, who need evidence-based counselling. Human papillomavirus (HPV) vaccination has shown very high protection rates against AGWs in clinical trials and real-world settings but vaccination coverage remains low in many countries. It is intended to support best practice in the care of patients with anogenital warts by including evidence-based recommendations on diagnosis, treatment, follow-up and advice to patients. It is intended for use by healthcare professionals in sexual healthcare or dermato-venereology clinics in Europe but may be adapted for use in other settings where the management of anogenital warts is undertaken.

Keywords: AGW, HPV, vaccination.

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Introduction:

An anogenital wart is a common superficial skin lesion in the anogenital area caused by specific human papillomavirus (HPV) genotypes 6 and 11 in >95% of cases Anogenital warts are also called condyloma acuminatum, genital warts, and venereal warts. **(1).**

Anogenital warts are usually a sexually transmitted infection, they are most commonly observed in young adults between the ages of 15 and 30 years. They are highly contagious. However, anogenital warts are rare in people who have been vaccinated against the benign HPV types in childhood before beginning sexual activity. Anogenital warts have been reported in a number of studies to be more common in males than females**. (2)**.

In most cases, the infection is asymptomatic and visible genital lesions develop only in a minority of those infected.

The incubation period between incident genital HPV infection and the

appearance of warts is highly variable but has been found to be shorter in women (median 2.9 months) than men (median 11.0 months) **(3).**

Clinical features of anogenital warts

An anogenital wart is a flesh coloured papule with a folded irregular surface. They can be as small as 1-5mm in diameter, but can also grow or spread into large masses in the genital or anal area. They may be hard or soft. Their color can be variable, and sometimes they may bleed. A linear pattern may be seen if the virus has been inoculated along a scratch or tear in the skin. Symptoms associated with anogenital warts can include: pain, bleeding, Itch and embarrassment**.(2)**.

They may be found anywhere in the anal or genital area, and are frequently found on external surfaces of the body, including the penile shaft, scrotum, or labia majora of the vagina. They can also occur on internal surfaces like the opening to the urethra, inside the vagina, on the cervix, or in the anus **(1).**

Anal canal warts are more common in men who have sex with men (MSM) reporting condomless anal intercourse or other sexual practices involving anal penetration. Perianal warts, however, are common in both sexes and can occur in the absence of a history of anal intercourse**(4).**

Complications

Psychosexual impact

The negative impact of genital warts on sexual activity and health related quality of life outcomes is well recognized.The condition may cause anxiety, guilt, anger and loss of self-esteem, and lead to concerns regarding future fertility and cancer risk **(5).**

Precancer and cancer

Anogenital warts are by definition benign lesions which pose no risk of neoplastic change. However, both premalignant (vulval, anal and penile intra-epithelial neoplasia, i.e. VIN, AIN, and PIN) or malignant lesions can coexist or develop within wart lesions or, rarely, be misdiagnosed as Warts. Clinical suspicion of neoplastic change should be aroused by bleeding or an atypical appearance including ulceration or palpable dermal infiltration. In such cases, urgent biopsy is warranted**(6)**.

Bowenoid papulosis is a condition characterized by reddish-brown lesions associated with oncogenic HPV types and is part of the clinical spectrum of anogenital intra-epithelial neoplasia**.(2).**

A rare variant of HPV 6/11 disease is the giant condyloma or Buschke–Lowenstein tumour. This is a form of verrucous carcinoma which causes local infiltration into underlying dermal structures. The mainstay of management is surgical resection with or without adjuvant chemoradiotherapy, topical retinoids or imiquimod. Specialist surgical and oncological involvement is required in these cases**. (7).**

Diagnosis

Cutaneous warts can generally be diagnosed by examining the affected area of skin. A good light source is recommended for examination. Magnification with a lens or colposcope may be useful for small lesions. Examination should include inspection of the urethral meatus . In female patients presenting with anogenital warts, vaginal or cervical warts are present in an estimated 15% and 6% of individuals respectively. Speculum examination should be offered at initial assessment if cervical or vaginal lesions are suspected, such as when lesions are found at the introitus or when the patient reports being aware of possible internal lesions.**(2)**

Perianal inspection should be offered for both sexes at initial assessment or if there are symptoms (e.g. lesions or anal irritation are reported); digital rectal examination and proctoscopy should be offered if anal canal warts are suspected (e.g. external lesions extending into the anal canal; anal bleeding or discharge)**(2)**.

Biopsy is not necessary for typical anogenital warts but is recommended if there is diagnostic uncertainty or suspicion of precancer or cancer.

The differential diagnosis of genital warts includes molluscum contagiosum and seborrhoeic keratoses as well as normal variants such as penile papules and Fordyce spots. Human papillomavirus detection or typing does not influence management and is not recommended**.(6)**.

The acetic acid test can be used to diagnose subclinical HPV lesions; its place in diagnosis and management is uncertain**(2)**.

Prevention

Food and Drug Administration (FDA) recommended 3 vaccines namely Gardasil®, Gardasil® 9, and Cervarix®. These HPV vaccines offer strong protection against HPV infection. It is suggested that before having sexual intercourse, every individual should take the HPV vaccine as early as 9 years old **(8).**

The vaccine is most effective in adolescents vaccinated before the first sexual contact, with an antibody production ten times higher than that found in the naturally acquired infection within two years. HPV vaccination does not result in changes in sexual behavior among adolescents.

Table (1): Presents the indications, doses for HPV vaccination **(9)**.

Table (1): Indications for vaccination against human papillomavirus infection **(9).**

Children and adolescents	People living with HIV, with solid organ transplants, bone marrow transplants, or people with cancer
Two doses (0 and 6 months)	Three doses (0, 2,and 6 months)
Girls from 9 to 14 years	Women from 9 to 26 years
Boys from 11 to 14 years	Men from

Male condom use

Use of male condoms is suggested for those with AGWs, having a partner with AGWs, or engaging in any sexual activity with new sexual partners as it helps decrease the risk of:

- Cervical and vulvovaginal HPV infections in women
- AGWs in men and women**.**

CIN2, CIN 3, and invasive cervical cancer in women **(10).**

- **Cervical Cancer screening**

Female patients should be educated about cervical cytology screening to avoid the progression of HPV-induced cancer cervix **(2).**

Counseling

Informing young adults and adolescents about HPV and the risks related to infection is an important consideration for the prevention of further increases in the incidence rates for HPV and genital warts **(10).**

Management

There is no cure for HPV. Existing treatments are directed towards the removal of visible warts, but these may also regress on their own without any therapy **(11).**

Recurrences occur after all therapies. Recurrence rates, including new lesions at previously treated or new sites, are often 20–30%, and increase with longer duration of follow-up.

All topical treatments are associated with local skin reactions including itching, burning, erosions and pain. **(12).**

Treatment algorithms

There is no single optimum treatment for anogenital warts. All modalities of treatment have advantages and limitations, and all are associated with a substantial risk of wart recurrence. Evaluation of the evidence is limited by the heterogeneity of study designs and reporting outcomes and a lack of head-to-head comparisons between treatments. Patient centred outcomes, in particular satisfaction with treatment, have been largely overlooked. Future studies should address these limitations (**13**).

Clinicians who treat anogenital warts should have access to a range of home and clinic-based therapies. Choice of therapy depends on the site, morphology and extent of warts and patient preference and requires discussion between the physician and the patient. Warts may regress spontaneously so that no treatment, or deferring treatment is a management option. Patients need to be advised, however, that lesions may get larger, or spread, and there may be an impact on the likelihood of transmission. Availability and cost may also dictate choice of treatment, and cost effectiveness will vary between healthcare systems .

A treatment that has antiviral effects on human papillomavirus would give more success and lower recurrence rates. One more problem for the patient is several visits to the hospital for treatment. This makes the

treatments not cost effective and sparing time may be hard for the patient too. Here, the treatments are discussed in three groups: self application treatments, treatments applied in the hospital, and alternative medical wart treatments **(14).**

Recommended treatments suitable for self-application:

Podophyllotoxin 0.5% solution (1A) and 0.15% cream (2A). Podophyllotoxin is self-applied to lesions twice daily for 3 days, followed by four rest days, for up to 4 or 5 weeks (according to the product licence). Common reactions include transient tenderness, erythema and erosions. Podophyllotoxin is contraindicated during pregnancy, and women of childbearing age must be advised to use an effective method of contraception or abstain from vaginal intercourse during therapy. The use of podophyllotoxin to treat perianal warts is outside the product licence for either preparation, but is well established in clinical practice. (**15).**

Clinical experience suggests that for ease of application the cream formulation is preferable for vulval and perianal warts, therefore we suggest the use of podophyllotoxin cream for warts at these sites. A mirror and digital palpation can facilitate the application procedure. Clearance rates of 36–83% for podophyllotoxin solutionand 43–70% for podophyllotoxin cream have been reported (**16)**

Imiquimod cream 5%: It is an immunomodulatory substance that induces a large number of cytokines, including from macrophages. One of the most frequently induced cytokines is interferon-alpha. Applied as a cream three times a week for 16 weeks, imiquimod achieves clearance rates between 16 % and 50 %. The most common adverse effects include local erosions, erythema, and a burning sensation. While the recently approved imiquimod 3.75 % cream demonstrates less pronounced local reactions in comparison to the 5 % cream, is also less effective (**2)**

Sinecatechins are derived from green tea leaves of the Camellia sinensis species containing the active ingredient epigallocatechingallate . The mechanism of action is uncertain but various immunomodulatory and antiproliferative properties have been proposed. EGCG is formulated as a 10% ointment. The ointment is applied three times daily until complete clearance, or for up to 16 weeks. It cannot be used for internal warts or in pregnancy. Side effects such as local skin reactions (itching, erythema), intensity, balanitis, herpes simplex, lymphadenitis, dysuria, rash, hyperkeratosis, skin discoloration, pain, and allergic dermatitis have been reported (**15)**.

Recommended clinic-based treatments

Cryotherapy. the simplest ablative treatment method is cryotherapy. Appropriate for the treatment of solitary genital warts, cryotherapy induces clearance rates between 80 % and 88 %, depending on the publication consulted. Recurrence of 25–40 %, even after multiple treatments.

Cryotherapy is performed every other week over a period of twelve weeks (**17)**

Cryotherapy has the advantage of being simple to deliver if the equipment is available, inexpensive and safe in pregnancy. Several recent studies have compared wart clearance rates with cryotherapy against other treatments including trichloracetic acid (TCA), imiquimod, CO2 laser and potassium hydroxide. Only CO2 laser resulted in superior wart clearance compared to cryotherapy **(18).**

Trichloracetic acid is a corrosive agent. It is applied directly onto the wart surface with either a wooden or cotton tipped applicator. It is usually applied weekly. It is most suitable for small acuminate or papular warts but less easy to use on keratinized and large lesions. Excess application may cause scarring therefore protection of surrounding skin with petroleum jelly is advised. A neutralizing agent (e.g. 5% sodium bicarbonate) should be readily available in case of spills. When used optimally, a shallow ulcer forms that heals without scarring. Clearance rates of 56–94%58, and a recurrence rate of 36%58 have been reported. TCA can be used safely during pregnancy **(18).**

Surgical treatment. A variety of surgical techniques are in use, including excision, electrosurgery, electrocautery and laser therapy. Surgery may be used as a primary therapy, and the majority of patients can be treated under local rather than general anaesthesia (e.g. 1–2% lidocaine for sub-cutaneous infiltration) (**19)**.

Electrosurgery, electrocautery and laser surgery should be performed with the use of surgical masks by the treatment team, and the use of an extractor fan due to the potential presence of infectious HPV particles in the smoke plume generated by these techniques**. (2)**

Excision under local anaesthetic using scissors, scalpel or curettage is an option when small numbers of lesions are present and for exophytic or pedunculated warts. With the use of diathermy to control bleeding, suturing may not be required. Clearance rates of 89–100% have been reported for scissor excision, with recurrence rates of 19-29%. **(18).**

Electrosurgery and electrocautery Modern electrosurgical units utilize alternating current to produce different types of waveforms resulting in blends of cutting and coagulation. There are two main approaches:

- Electrocautery (also known as electrofulguration): the passage of a direct or alternating electric current through a resistant electrode tip which generates heat, the application of which leads to immediate tissue destruction. Any eschar can be removed with a curette.
- Electrosurgery (including hyfrecation): involves passing a high frequency alternating electrical current directly through an electrode tip. Direct contact

of the tip with the lesion causes cutting and coagulation. Electrodessication is achieved by maintaining an air gap (1–3 mm) between the electrode tip and the lesion, leading to heating and carbonization of the tissue. As with electrocautery, any eschar can be removed with a curette**.(20)**

- Clearance rates of 94–100% and recurrence rates of 22% have been reported.

- Laser surgery uses a concentrated beam of infrared, or near infrared, light energy to heat and cauterize the affected area, and allows very high power densities to be delivered to small tissue volumes. The carbon dioxide (CO_2) laser and the neodymium–yttrium aluminium garnet (Nd-YAG) laser are in widespread use.79 Clearance rates of close to 100% are usual although recurrence rates of 17–19% at 12 weeks and 66% at 12 months are comparable to other treatment modalities **(21).**

- **Alternative Medical Wart Treatments:**

5-fluorouracil : 5-fluorouracil (5FU) is an anti-metabolite which blocks DNA synthesis. It is available as a 5% cream which is used to treat neoplastic and preneoplastic skin conditions including Bowen's disease and superficial basal cell carcinoma **(2)**

Intralesional/topical interferon .There is no evidence for the use of systemic interferon for anogenital warts84,85; however, studies of locally administered interferon, mostly using interferon alpha, have yielded some positive results. (**22)**

Human Papilloma Virus (HPV)Vaccine HPV vaccines target high-risk HPV types in the prevention of associated cancers. Although they do not target common warts, there are studies that found them effective for treating extragenital warts. Although there are not sufficient studies with a large number of patients, it may be an option for recalcitrant warts, even in immunosuppressed patients (**23**)

Bleomycin Intralesional bleomycin treatment has been used on resistant warts. The most common dosing schedule was using 1 U/mL solution, up to 1-2 mL per treatment. It can be performed intralesionally up to 4 times at 2-3-week intervals. The side effects are eschar formation and hyperpigmentation and flagellate hypopigmentation (**24**)

Photodynamic therapy: Photodynamic therapy (PDT) employs topical 5-aminolevulinic acid (ALA) as photosensitizer, followed by irradiation with red light to induce cell death or immunomodulation through generation of reactive oxygen species. Its uses include the treatment of actinic keratoses, basal cell carcinomas and Bowen's disease **(25).**

Combination therapies: Treatments have often been used in combination. There is some theoretical rationale; for example, initial use of an ablative therapy may enhance local penetration of subsequent

topical treatment, particularly for keratinized warts. Nonetheless, there is a lack of clinical trial evidence. In one placebo-controlled study, adjuvant podophyllotoxin cream following cryotherapy did not improve wart clearance at 4, 12 or 24 weeks post-treatment initiation. Further evaluation of such treatment approaches is warranted, given the limited efficacy of most treatments and the frequency of recurrence (**2).**

Immunotherapy, which is based on the stimulation of the immune system to deal with the virus and suppress its activity. Immunotherapy may be applied either topically or through intralesional injection or systemic administration **.**The selection of the most appropriate means of immunotherapy is usually difficult. Many factors should be considered before the treatment of the patients, such as age, sex, past medical history, and the clinical characteristics of warts. People with multiple warts or warts resistant to treatment are usually prone to have a defective cell-mediated immune response **(26).**

Several immunomodulating agents have been assessed for the treatment of genital warts which involve topical imiquimod, interferon- α2b (IFN- α2b), and skin test antigens **(27) (Table 2)**.

The specific intralesional immunotherapies that have been studied include: *Candida albicans*; measles, mumps, and rubella; *Trichophyton*; and tuberculin antigens such as purified protein derivative, Mycobacterium w vaccine, and Bacillus Calmette-Guerin. Intralesional vaccine injection represents a safe, effective, and tolerable treatment for warts, including recalcitrant and anogenital warts (**26).**

Generally, the results of immunotherapy have been highly variable among individuals but the method is highly promising due to its activity beyond the injected wart and so, a significant number of patients are cured of distant warts. Adverse reactions reported are usually minimal; flu-like symptoms, responding to nonsteroidal anti-inflammatory agents (NSAIDs) **(26).**

Table (2): Various agents used for immunotherapy of genital warts **(27).**

Dose, administration	**Agent**
Topical agents:	
▪ 5% cream, 3times per weak, for 16 weeks	**Imiquimod**
▪ applied topically on warts in normal saline or salicylic acid, washed after 2 hours, weakly treatment for 6-12 weeks	**BCG**
Intralesional agents:	
▪ 0.1 -0.5ml intralesional injection in largest wart, in 2weaks interval for 5 sessions	**BCG vaccine**
▪ 0.1ml weakly intradermal injection in the forearm for 12weaks	**PPD**

▪ 0.3 ml injection in largest wart every 3 weeks, maximum 5 sessions.	**Trichophyton antigen**
▪ 1-2 million units3days per weak(Monday-Wednesday- Friday) for 3 weeks	**Interferon alfa 2B**
▪ 0.3-0.5 ml into the single large wart for up to 5 sessions	**MMR vaccine**
▪ 0.1-0.3 ml injected in the largest wart in 1st setting, then 3weakly intralesional injections	**Candidal extract**
systemic Interferon	

Therapies not generally recommended

Podophyllin. Podophyllin 20–25%, a non-standardized resin extract from the Podophyllum plant, is inexpensive to produce but is less effective than podophyllotoxin. Podophyllin preparations contain a variety of compounds some of which may be mutagenic and severe systemic toxicity after topical use has been described including death (**2).**

Treatment in pregnancy

In pregnancy, warts may enlarge and multiply. Topical treatments should be avoided but ablation using cryotherapy, TCA or any surgical treatment modality is acceptable. The presence of warts rarely impacts on the mode of delivery unless there is obstruction of the birth canal due to very large warts. Liaison with the obstetrician in management is recommended in all cases. Spontaneous regression of genital warts is frequently seen in the puerperium. Delaying treatment until after delivery is common practice. (**2)**

Treatment in immunocompromized patients

Both HIV infection and other causes of systemic immuno-suppression are associated with an increased incidence of warts. Moreover, the response to treatment in HIV-positive subjects is impaired, and recurrences after treatment are more common (**2).**

Partner notification

Current partners of patients with anogenital warts should be offered clinical assessment for the presence of warts along with education and advice about HPV infection and screening for other sexually transmitted infections **(28).**

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