1. RATIONALE AND OBJECTIVES

The main purpose of the Spanish Association of Cervix Pathologies and Colposcopy (Asociación Española de Patología Cervical y Colposcopia – AEPCC) is to “promote the knowledge and research of women’s lower genital tract”. To fulfil this objective, and sensitive to the demand of professionals dedicated to lower genital tract pathologies and colposcopy, the AEPCC has created the “AEPCC-Guidelines” (AEPCC-guías).

The AEPCC-guidelines cover specific areas of knowledge of the lower genital tract pathology characterized by their relevance and important impact on clinical practice. AEPCC-guidelines are scientific evidence-based documents which are systematically developed and are intended to help professionals to reach a consensus on clinical practice decision-making about the most appropriate diagnostic and therapeutic options of a particular health problem.

The specific objectives of the AEPCC-guidelines are:

- Promote standardized lines of action based on the current scientific evidence and on reliable and agreed information.
- Ensure the equality of patients at the time of being take care of, regardless of their location, thus promoting good practice.
- Improve the effectiveness of interventions and the quality of health care.
- Favour the implementation of quality control or clinical efficacy indicators
- Facilitate decision-making in the administrative field for managers and planners of health resources.

Ultimately, the methodological rigor established for the preparation of AEPCC-guidelines pursues creating documents of outstanding scientific quality whose implementation allows a better clinical practice and a greater knowledge of the lower genital tract pathology.

2. METHODOLOGY

The specific methodology that has been followed for the preparation of AEPCC-guidelines includes the following aspects:

- The AEPCC Steering Committee will appoint a coordinator responsible for the preparation of the AEPCC-guidelines. This Coordinator, in accordance with the Steering Committee, shall appoint the writing Committee consisting of him/herself, a Secretary and the participants. The members will be professional experts who are members of the AEPCC or other scientific societies with recognized prestige on this topic
- Consensual development of the index.
- Critical review of the available literature and assignment of levels of evidence.
- Discussion and consensus among the committee members for assigning the grade of recommendation.
- Writing the document
- Final analysis of the document by a Review and Editing Committee
- Print and online format of the final version.
- Dissemination of the AEPCC-guidelines in congresses, courses and seminars organized by the AEPCC.
- Development of online courses on the contents of the AEPCC-guidelines that allow a detailed knowledge of these guides and facilitate their implementation in the daily clinical practice. (training credits)
- Update of the AEPCC-guidelines.
2.1 Assessment of the scientific evidence and extent and strength of the recommendations. The GRADE System.

“Clinical practice guidelines” consist of recommendations addressed to healthcare professionals to help them in the patient’s care in relation to a particular clinical condition. They are based on the most important literature on a certain topic (systematic reviews of the medical literature and identification of studies with greater scientific evidence) and on practical clinical experience. In general, prospective studies in which patients have been randomly assigned are granted the highest level, whereas data obtained from the opinion of experts receive the lowest level. In this way it is possible to assess the quality of the evidence associated with the outcomes of a particular strategy. For the preparation of AEPCC-guidelines all the recommendations made have taken into account the quality of the current scientific literature. The strength of the recommendation has been agreed upon by the responsible Committee of the AEPCC-guidelines depending on the quality of the available works.

For the classification of scientific evidence and the extent and strength of recommendations the GRADE (Grading of Recommendations Assessment, Development and Evaluation Working Group) system (http://www.gradeworkinggroup.org/) has been used.

To do this the following steps have been followed:

1. **Framing the PICO (patient, intervention, comparison, outcomes) questions** and defining outcome variables (in terms of benefit and risk) for each of the intervention questions asked.

2. **Scoring outcome variables from 1 to 9.** The key outcome variables relevant for making a decision had a score of 7 to 9; for important variables (but not key), 4 to 6, and for those less important variables, from 1 to 3. The Working Group identified, assessed and agreed upon the importance of the outcome variables.

3. **Evaluation of the quality of the evidence for each of the key outcome variables.** Search strategies were designed to identify systematic reviews and randomized clinical trials and other studies published. The quality of the evidence for each variable in the GRADE system was assessed as high, moderate, low and very low. The randomized clinical trials and systematic reviews of randomized clinical trials have as a starting point a high quality of evidence and the observational studies and systematic reviews of observational studies a low quality of evidence. The aspects which allowed decreasing or increasing the quality of evidence are described in table I.

4. **Assessment of the overall quality of evidence.** The overall quality of evidence was based across outcomes based on the lowest quality of evidence achieved for key outcome variables. In cases in which evidence for all the key variables favoured the same alternative and there was evidence of high quality for some, but not for all variables, the overall quality was considered as high. Low quality evidence on unimportant benefits and risks did not decrease the global evidence grade.

5. **Assigning a strength to the recommendation.** The GRADE system differentiates between strong and weak recommendations and makes explicit judgments about the factors that may affect the strength of the recommendation: balance between benefits and risks, overall quality of evidence, values and preferences of the population and costs. Both categories, strong and weak, may be for or against a particular intervention. Table II describes the meaning of the strong and weak categories.
### Table 1: GRADE system for assigning the quality of evidence

<table>
<thead>
<tr>
<th>Study design</th>
<th>Initial quality of evidence</th>
<th>In clinical trials, decrease if *</th>
<th>In observational studies increase if</th>
<th>Final quality of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomized clinical trials</td>
<td>High</td>
<td>Critical (-1) or very important (-2) limitation to study quality</td>
<td>Consistent and direct strong association** without confounding factors</td>
<td>High</td>
</tr>
<tr>
<td>Observational study</td>
<td>Low</td>
<td>Important inconsistency (-1) Some (-1) or major (-2) uncertainty about directness of evidence</td>
<td>Very strong evidence** without major threats to validity (no evidence) and direct evidence (+2).</td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Imprecise or sparse data</td>
<td>Dose response gradient (+1)</td>
<td>Low</td>
</tr>
<tr>
<td></td>
<td></td>
<td>High probability of reporting bias (-1)</td>
<td>All plausible confounders could have reduced the observed effect (+1)</td>
<td>Very low</td>
</tr>
</tbody>
</table>

* Increase (+1) or decrease (-1) a level (e.g. from high to moderate); 2, increase (+2) or decrease (-2) two levels (e.g. from high to low)

** A statistically significant relative risk > 2 (<0.5) based on evidences consisting in two or more observational studies without plausible confounders.

*** A statistically significant relative risk > 5 (<0.2) based on direct evidence and without major threats to validity.


### Table 2: GRADE system for assigning strength to recommendations

<table>
<thead>
<tr>
<th>Strong</th>
<th>Weak</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patients</strong></td>
<td>Most people would agree on the recommended course of action and only a small number would not.</td>
</tr>
<tr>
<td><strong>Clinicians</strong></td>
<td>Most patients should receive the intervention recommended</td>
</tr>
<tr>
<td><strong>Managers/policy makers</strong></td>
<td>the recommendation can be adopted as a policy in most situations</td>
</tr>
</tbody>
</table>

Participants

CONDYLOMA ACUMINATA

COORDINATOR

Dr. Jesús de la Fuente Valero
Gynecology and Obstetrics Unit. Low Genital Tract Pathology Unit. Hospital Universitario Infanta Leonor. Madrid.

REVIEWERS - EDITORS

Dr. Aureli Torné Bladé
Gynaecological Oncology Unit, Instituto Clínico de Ginecología y Obstetricia y Neonatología (ICGON), Hospital Clinic. Instituto de Investigaciones Biomédicas August Pi i Sunyer (IDIBAPS), Facultad de Medicina, Universidad de Barcelona, Barcelona, España

Dra. Marta del Pino Saladrigues
Gynaecological Oncology Unit, Instituto Clínico de Ginecología y Obstetricia y Neonatología (ICGON), Hospital Clinic. Instituto de Investigaciones Biomédicas August Pi i Sunyer (IDIBAPS), Facultad de Medicina, Universidad de Barcelona, Barcelona, España.
AUTHORS

Dra. María Brotons Agulló
Especialista en Medicina Preventiva y Salud Pública.

Dra. Amina Lubrano Rosales

Dr. Alfonso Alba Menéndez
Biólogo especialista en Biología Molecular. Unidad de Oncología Molecular. Instituto de Estudios Celulares y Moléculares de Galicia. Lugo.

Dra. Rosa Guarch Troyas

Dra. María Serrano Velasco

Dr. Jesús de la Fuente Valero

Dr. Juan Ballesteros Martín

Dr. Pere Fusté Brull
Unidad de Ginecología Oncológica, Instituto Clínico de Ginecología y Obstetricia y Neonatología (ICGON), Hospital Clinic. Barcelona. Facultad de Medicina, Universidad de Barcelona.

Dra. Elena Sendagorta Cudós
Servicio de Dermatología. Hospital Universitario La Paz. Madrid.

Dra. Gema Aguión Gálvez

Dr. Juan José Hernández Aguado
# CONDYLOMA ACUMINATA

## TABLE OF CONTENTS

1. INTRODUCTION .......................................................... 09
2. EPIDEMIOLOGY ........................................................ 10
  2.1 Disease Burden ........................................................ 10
  2.2 Social, Health and Economic Impact .......................... 11
3. ETIOPATHOGENESIS ............................................... 12
  3.1 Etiology ............................................................. 12
  3.2 Routes of Transmission ........................................... 12
    3.2.1. Sexual ......................................................... 12
    3.2.2. Vertical ...................................................... 12
    3.2.3. Other .......................................................... 12
  3.3 Risk Factors and Behaviours .................................... 13
4. NATURAL HISTORY .................................................. 14
5. HISTOLOGY ............................................................ 15
6. CLINICAL CHARACTERISTICS .................................... 16
7. DIAGNOSIS ............................................................ 17
  7.1 Clinical Examination ............................................ 17
  7.2 Biopsy .................................................................. 17
  7.3 Molecular Diagnostics ............................................ 17
  7.4 Differential Diagnosis .......................................... 17
  7.5 Condylomata as a Risk Marker of Precancerous Lesions of the Genital Tract ........................................... 18
  7.6 Extrapapillary Examination (Oropharynx and Anus) ... 18
8. TREATMENT ............................................................. 20
  8.1. General Principles ............................................... 20
  8.2. Cytotoxic Agents .................................................. 20
    8.2.1. Podophyllotoxin ........................................... 20
    8.2.2. Trichloroacetic acid (TCA) ............................... 21
  8.3. Immunomodulators .............................................. 21
    8.3.1. Imiquimod ..................................................... 21
    8.3.2. Sinecatechins (Polyphenon E) ............................ 22
  8.4. Excision ............................................................ 22
  8.5. Ablation ............................................................ 23
  8.5.1. Cryotherapy .................................................. 23
  8.5.2. CO2 laser ........................................................ 23
  8.5.3. Diathermy electrocoagulation ............................. 23
  8.6. Other investigational treatments ............................. 24
    8.6.1. Photodynamic Therapy (PDT) ............................. 24
    8.6.2. Cidofovir ..................................................... 24
  8.7. Quality of Evidence and Recommendations for Treatments Commonly Used in Non-Pregnant Immunocompetent Women According to the GRADE System .................................................. 25
  8.8. Treatment under Special Circumstances .................. 25
    8.8.1. Pregnancy ..................................................... 25
    8.8.2. Immunosuppression ....................................... 25
    8.8.3. Childhood ................................................... 26
  8.9. Treatment of Condylomata in Other Areas of the Genital Tract .................................................. 26
    8.9.1. Vagina .......................................................... 26
    8.9.2. Cervix .......................................................... 26
    8.9.3. Anus ............................................................ 26
  8.10. Treatment Algorithm .......................................... 27
9. POST-TREATMENT FOLLOW-UP ................................. 28
10. PRIMARY PREVENTION OF CONDYLOMATA. PROPHYLACTIC VACCINES AGAINST HPV ................................. 29
11. RECOMMENDATIONS ............................................... 32
12. REFERENCES ........................................................ 33
Condyloma acuminata (CA) or genital warts (GW) are the clinical expression of infection by certain types of human papilloma virus (HPV) that are associated with a low oncogenic risk. Currently, condyloma acuminata are considered to be one of the most common sexually transmitted diseases, with growing incidence among most populations. Although this disease is one of the non-neoplastic processes caused by HPV, and therefore, is classified as benign, it is of great clinical significance for several reasons. Specifically, the physical, emotional, and psychosexual impact of this disease and the connotations associated with sexual transmission among female patients is significant.

Moreover, the clinical approach towards these patients in clinical practice is challenging. Firstly, the forms of presentation and extension of the lesions vary widely, from very localized forms with low disease volume, to very extensive forms involving multiple foci in the anogenital tract. Secondly, no single therapy is effective in all patients, so the healthcare professional must tailor treatment and make a choice from the various available procedures (excision, ablation, topical therapy, etc). Thirdly, the rate of relapse after treatment, when new lesions appear in treated or untreated areas, remains high. Finally, the healthcare and economic burden of the diagnosis, treatment and follow-up of women with condyloma acuminata is significant, given the high prevalence of the disease and the costs associated with clinical care.

The aim of these AEPCC guidelines is to provide a detailed review of all aspects of condyloma acuminata. This standardized information should be useful for healthcare professionals when taking decisions based on the best available evidence and state-of-the-art knowledge.
2. Epidemiology

2.1. DISEASE BURDEN

HPV genital infection is one of the most common sexually transmitted infections. However, condyloma acuminata are not included in the disease surveillance systems of most countries, so worldwide epidemiological data are limited. Moreover, the estimated disease burden is based on studies conducted in individuals who consult due to condyloma acuminata, so rates may be underestimated. A systematic review showed that the incidence of new cases (in both men and women) ranges between 118 and 205 per 100,000 inhabitants, and the total annual incidence (including new and recurrent cases) is between 160 and 289 per 100,000 inhabitants. The highest incidence rates are observed in women between the ages of 20 and 24 years, and in men between the ages of 25 and 29\(^1\). The prevalence of these lesions in studies examining administrative databases or clinical records is 0.15%-0.18\(^1\).

Time-trend data show an increase in condyloma acuminata in several countries (Canada, U.S., U.K., Netherlands, and Nordic countries) in the period before the introduction of national HPV vaccination programs (2007-2008)\(^1,2\). Since then, countries that administered the tetravalent vaccine (such as Australia, Denmark, Sweden, and U.S.) have recorded a significant reduction in the incidence of this disease\(^3-6\).

In Spain, condyloma acuminata are not listed as a “Disease of Compulsory Declaration” (DCD), except in Catalonia, where it has been considered a numerical EDO since 2007, although no overall Spanish surveillance system is in place. A retrospective study performed in 2005 in six Autonomous Communities estimated an incidence of 118 new cases per 100,000 inhabitants between 14-64 years of age (137 per 100,000 men and 100 per 100,000 women)\(^7\). Estimated prevalence was 182 per 100,000 inhabitants aged 14-65 years (203 per 100,000 men and 162 per 100,000 women)\(^7\).

Catalonia is the only autonomous community that collects time-trend data. These data confirm that the number of condylomata declared via the DCD system rose between 2007 and 2014\(^8\), although this increase, particularly in 2007-2011, may have be due to an improved surveillance system.

Adapted from SIVES 2015
(Integrated AIDS/HIV/STD Epidemiologic Surveillance System of Catalonia) 8

Figure 1 shows the number of condyloma acuminata cases reported to the DCD registry from 2011 to 2014.
2.2. SOCIAL, HEALTH AND ECONOMIC IMPACT

The psychosocial, healthcare and economic impact of condyloma acuminata is significant. In addition to pain, bleeding and pruritus, patients often present psychosocial or psychosexual symptoms, including shame, anxiety, sexual dysfunction, or low self-esteem. According to a recent study in the UK, condyloma acuminata have a negative impact on health-related quality of life of patients, and a psychosocial impact that is even greater than that of precancerous cervical or vulvar lesions. Moreover, patients may relapse despite treatment.

The diagnosis, follow-up, and treatment of condyloma acuminata add up to a considerable healthcare cost. Castellsagué et al. estimated that in 2005 in Spain the mean direct cost of treatment of condyloma acuminata and associated complications was €833 per patient, and the indirect cost was €1,056, significantly higher in women than in men (€1,040 and €1,223, respectively). Total estimated costs were €47 million (direct costs) and €59.6 million (indirect costs). Studies from other countries have reported lower treatment costs, but the results are difficult to compare due to differences in populations, study methodologies, and the use of country-specific costs.

<table>
<thead>
<tr>
<th>KEY CONCEPTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>The highest incidence rates of condyloma acuminata occur in individuals between the ages of 20 and 29 years.</td>
</tr>
<tr>
<td>In the period before HPV vaccination, the incidence of condylomata was increasing in several developed countries.</td>
</tr>
<tr>
<td>After the introduction of vaccination programs using the tetravalent HPV vaccine, several countries detected a significant reduction in the incidence of condyloma acuminata.</td>
</tr>
<tr>
<td>Condyloma acuminata involve substantial healthcare costs.</td>
</tr>
</tbody>
</table>
3. Etiopathogenesis

3.1. ETIOLOGY

HPV is the causative agent of condyloma acuminata, 95% of which are caused by genotypes 6 and 11. Other more rare genotypes are: 8, 13, 30, 32, 42, 43, 44, 54, 55 and 70. Up to 20-30% of cases present with coinfection with other HPV types with high oncogenic risk. Although condyloma acuminata have been anecdotally reported to become malignant, some authors suggest that this may be due to coinfection with other condylomata with increased risk of anogenital and cervical neoplasia. Moreover, the presence of genotype 6 (subtype 6b) and to a lesser extent genotype 11 is well documented in Buschke–Löwenstein condyloma, a rare verrucous carcinoma of the anogenital skin. This is a histologically well-differentiated tumour, but its local destructive potential is high, so it can show malignant behavior.

HPV has a particular predilection for the skin and mucous membranes. Infection generally occurs via small fissures in the epithelial surface that allow the virus to penetrate the basal keratinocytes. This infection is characterized by a lack of cytolysis and systemic phase, which reduces its antigenic potential. HPV uses the replication and differentiation mechanisms of the epithelial cells for its own replication and assembly. The cytopathic effect of viral replication causes cellular vacuolation (koilocytosis). Finally, during the epithelial desquamation phase, new virions are released to infect neighbouring cells, leading to viral and epithelial proliferation, which manifests clinically as a condylomatous lesion. Most of these infections are latent or subclinical, and resolve spontaneously. However, a small percentage persists and produces proliferative lesions in the skin and mucous membranes.

Condyloma acuminata are characterized by a high transmission rate of around 65% between an infected sexual partner and a susceptible sexual partner. The incubation period ranges between 3 weeks and 8 months, and the mean time until lesions appear after infection is 2 months, making condyloma acuminata the first clinical marker of (sub)acute HPV infection.

3.2. ROUTES OF TRANSMISSION

3.2.1. Sexual

Condyloma acuminata are transmitted by direct contact of skin or mucosa, from a partner who has visible or subclinical condyloma acuminata. The main route of transmission is vaginal or anal coitus. Receptive anal sex has been closely associated with the development of condylomata in the anal passage of homosexual and bisexual men, and to a lesser extent in women. Some anal and perianal lesions may be caused by viral excretion from vaginal secretions and not by anal sex. HPV is considered a field infection, and can affect any part of the lower genital tract.

If condyloma acuminata is detected in childhood, the possibility of sexual abuse should be ruled out.

3.2.2. Vertical

The risk of vertical transmission during the perinatal period or persistent infection in the newborn is very low. The route of transmission may be intrauterine, via the birth canal, or even postnatal. The greatest risk of transmission for the newborn is maternal history of genital condylomatosis during pregnancy, but not the passage through the birth canal during delivery. Cesarean section, then, is not indicated to terminate gestation in a woman with genital condylomatosis, unless the birth canal is obstructed by lesions or vaginal delivery might cause excessive bleeding.

3.2.3. Other

Other routes of genital transmission without penetration are uncommon. Oral and digital transmission of some types of genital HPV can occur, but the risk of infection from digital-genital or oral-genital contact appears to be minimal. No firm evidence is available on the fomite transmission of condyloma acuminata.
3.3. RISK FACTORS AND BEHAVIOURS

The main risk factors for acquiring HPV infection are a high number of sexual partners or young age at first coitus. Other factors have been described, such as tobacco consumption, coexistence of other sexually transmitted diseases, no condom use, low educational level, and sexual contacts with uncircumcised males. The biological explanation for the increase in risk associated with tobacco use is based on an altered immune response to HPV observed in smokers, due to reduced levels of S-100 and CD1a-positive Langerhans cells.

Immunosuppression is also associated with a higher rate of condyloma acuminata and precancerous and cancerous cells in the genital tract. The relative risk of cervical cancer is 4-fold higher in immunosuppressed patients with condylomata. Cytokine production in the epithelial cells of these patients is abnormal, accelerating, on the one hand, the course of established infections, and on the other, reactivating latent HPV infections. Moreover, cytotoxic T cells in these patients have also shown a reduced reactivity against viral oncoproteins E6 and E7. Despite the above, no major risk of carcinogenic transformation of condyloma acuminata has been observed in immunosuppressed patients. In HIV-positive patients, active antiretroviral treatment is associated with a lower rate of condyloma acuminata.

### KEY CONCEPTS

| Condyloma acuminata are the mucocutaneous manifestation of (sub)acute HPV infection, generally by subtypes 6 and 11. |
| The main route of transmission is sexual contact. |
| Main risk factors are number of sexual partners and young age at starting sexual relations. |
| This is a very common disease in immunosuppressed patients. |
After HPV infection (introduction of viral DNA in the basal epithelial cells) and after a period of latency estimated at between 3 weeks and 8 months\textsuperscript{28}, episomal forms of viral DNA particles begin to be expressed, triggering a series of events leading to the development of lesions. A study published in 2005 establishes the annual risk of developing condyloma acuminata after initial infection to be 28.5\%\textsuperscript{29}.

If it is to persist, the viral infection must evade the non-specific and specific immune response. HPV will try to avoid detection and elimination of the viral cells by the immune system. These evasion processes are activated by different pathways. In the case of evasion of the non-specific immune response, a marked reduction in the number of Langerhans cells has been observed, with the consequent loss of antigen-processing capacity. A significant reduction in the activity of natural killer (NK) cells with non-specific immune functions has also been reported\textsuperscript{30}.

Once the epithelium has been infected, recognition of HPV by the immune system mobilizes a specific immune response. This may be humoral (generating antibodies for subsequent contact with the same pathogen) and cellular (used to eliminate infected cells). The physiological clearance of condylomatous lesions depends on the second type of immunity involved, cell-mediated immunity.

Untreated condyloma acuminata can resolve spontaneously, remain unchanged, or increase in number and/or size\textsuperscript{31}. Due to the lack of well-designed studies, controversy persists surrounding the similarity of rates of HPV regression in the context of cervical squamous intraepithelial lesions (SIL), with those of condyloma acuminata. In the literature we can find regression figures of up to 37.5\% of cases in a period of 20 weeks\textsuperscript{32}.

Certain physiological immunosuppressive states, such as pregnancy, promote the progression of condylomata, often to an alarming extent. Immunosuppression caused by other diseases or infections, such as HIV, also affects the progression of condylomatous lesions. In the case of HIV infection, one of the major mechanisms shown to affect the progression of lesions is the low production of interferon by NK cells, due to the reduced proportion of CD4 lymphocytes. All diseases that affect these biological pathways, such as primary T cell immunodeficiency or idiopathic CD4 lymphopenia, have similar clinical manifestations. In contrast, stimulation of the T-1 helper cell pathways, stimulating cytokine production, significantly influences the physiological clearance of the infection.

**KEY CONCEPTS**

1. The latency period between initial infection and the appearance of lesions ranges from 3 weeks to 8 months.

2. Untreated condyloma acuminata can resolve spontaneously, remain unchanged, or increase in number and/or size.

3. Physiological immunosuppressive states, such as pregnancy, promote the progression of condylomata.
The life cycle of HPV is intimately dependent on the maturation process of the squamous epithelium. The characteristic cytological change in mature cells is koilocytic atypia or koilocytosis (nuclear atypia and perinuclear vacuolation), called the "cytopathic" viral effect\(^3\). Condyloma acuminata can present various different cytohistological changes, many of which coexist in the same lesion. The classic form consists of proliferations of squamous epithelium with a papillary architecture (papillomatosis) and presence of acanthosis, hyperkeratosis, parakeratosis, and more specifically, koilocytic atypia. The second form of presentation, and the most common, involves all the above-mentioned features, but without cytopathic changes. The presence of papillomatosis and acanthosis are considered sufficient to determine a diagnosis of condyloma, since these findings are strongly associated with HPV infection\(^4\).

The third form of histological presentation involves proliferation of basaloid-type cells, corneal cysts, and minimally prominent koilocytosis. Histological findings of this form of presentation are similar to those of seborrhoeic keratosis (it differs from the latter by its association with HPV)\(^5-36\). The fourth category consists of flat lesions or lesions with discrete acanthosis and minimal nuclear atypia.

Histologically, the differential diagnosis of condylomata should consider several entities: 1) fibroepithelial polyps, 2) distal or introital vaginal mucous membrane folds, hymenal ring remains that present with minimal acanthosis, and stromal cell atypias, unrelated with HPV\(^4\), 3) verruciform xanthoma, 4) acantholytic dyskeratosis, 5) multinucleated cells associated with unspecific inflammatory changes, characterized by the presentation of normal-sized nuclei\(^4\), 6) vulvar intraepithelial neoplasia (VIN), characterized by papillomatosis and koilocytic changes (presence of atypia and mitosis throughout the whole epithelial thickness, differentiating the lesions from condyloma acuminata)\(^42\). Neoplasms should also be ruled out by assessing for the presence of marked cytological atypia, abnormalities in squamous differentiation and clinical history in older patients with inflammatory dermatosis, along with the classic features of condyloma acuminata.
Symptoms associated with condyloma acuminata depend mainly on the site, number, and size of the lesions. In a recent Spanish multicenter study, in which 123 gynaecology departments responded to a survey on condyloma acuminata in the lower genital tract and perianal area, the most frequent symptom was pruritus, followed, in order of frequency, by increased leucorrhea, feeling of discomfort, bleeding, and pain.

In the mucosa of the cervix and the vagina, the course of condyloma acuminata is generally asymptomatic, rarely causing dyspareunia, leucorrhoea, pain, burning sensation, or bleeding during coitus.

In the vulvar area, condyloma acuminata may cause pruritus, local hypersensitivity, burning, or occasional bleeding. In exceptional cases in which the patient has numerous, large lesions (immunosuppressed patients), the discomfort may be significant. In these situations, the patient may report difficulty and discomfort during personal hygiene activities and sexual relations.

If the condyloma acuminata are located in the urethral meatus, a site that is more unusual in women than in men (4%-8%), they may even obstruct the passage of urine.

However, in most cases, symptoms in the anus are generally mild or absent. However, patients with a high number of large lesions may have difficulties with personal hygiene or passing stools. In areas other than the genitals, such as the mouth, and in other exceptional sites, such as the conjunctiva or the nasal cavity, symptoms will again depend on the number and size of lesions.

During gestation, a special state of immunological tolerance occurs, which, together with the hormonal effects of progesterone and vascular changes, causes a poorer immunological response to HPV. For this reason, during pregnancy, the size and number of condyloma acuminata may also be larger than usual, and on rare occasions may even prevent vaginal delivery.

The psychological status of women with condyloma acuminata deserves special mention. They are frequently worried, embarrassed, have low self-esteem, and their sex lives are affected. This entity must be given the necessary importance, and it is essential that patients are given appropriate, reassuring information.

<table>
<thead>
<tr>
<th>KEY CONCEPTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms depend on the site, number, and size of the lesions.</td>
</tr>
<tr>
<td>Women with condyloma acuminata (CA) may present dyspareunia, leucorrhoea, burning sensation in the genitals, or bleeding during sex.</td>
</tr>
<tr>
<td>This disease must be given the necessary importance, and it is essential that patients are given appropriate, reassuring information.</td>
</tr>
</tbody>
</table>
7. Diagnosis

7.1. CLINICAL EXAMINATION

Diagnosis of condyloma acuminata is based primarily on physical examination, for which appropriate lighting and a magnifying glass or colposcope are needed for the detection of small lesions. The use of acetic acid in the vulva, vagina and/or cervix to reveal smaller condyloma acuminata is not a standard practice as it can lead to false positive diagnoses.

In the vulvar and perianal area, the presentation of condyloma acuminata varies widely. Most often, between 5 and 15 lesions, isolated or in plaques, are found, either pedunculated or with wide bases, sized between 1 and 10 mm each, more or less raised, with a spiculated (formations similar to crests) or flat surface. In general, the surface of the lesions loses the spiculated aspect over time, and becomes more smooth and rounded, and the colour changes from an initially pinkish tone (due to hypervascularization) to a more pigmented tone, which can even turn brown. When keratinization is predominant, lesions turn a whitish gray color.

In the mucosa of the cervix and the vagina, condyloma acuminata usually present as one or more raised pinkish lesions, with a wrinkled surface, pedunculated or sessile. On occasions, they present on first sight as white plaques, or less frequently as hyperpigmented macules or papules. Lesions frequently occur in multiple sites, so if condyloma acuminata are detected in the anovulvar area, the vagina and the cervix should be examined.

7.2. BIOPSY

Indications

1) Suspicion of precancerous (VIN, VaIN, etc.) or neoplastic disease; 2) worsening of lesions during treatment (poor treatment response despite good compliance).

Technique

First, the area to be biopsied must be appropriately disinfected. Then, the area where the biopsy is to be performed must be infiltrated or sprayed with a local anaesthetic agent. The biopsy can be obtained by punch biopsy (similar to that used on the cervix and vagina), swab, or Keyes punch biopsy.

After biopsy, bleeding will be stopped by the application of pressure to the area for 3 minutes and use of haemostatic agents (silver nitrate, ferric chloride, or Monsel’s solution). If these interventions are insufficient and bleeding persists, which is unusual, the wound may be sutured. In this case, the fewest sutures possible must be applied, using small diameter absorbable thread.

7.3. MOLECULAR DIAGNOSTICS

HPV determination is not indicated in patients with condyloma acuminata, since this does not add clinical information nor does it modify the approach to such lesions. It may be indicated in the paediatric population only, since it is often necessary to rule out or confirm the existence of HPV, due to the possible association between HPV infection and sexual abuse of the minor.

Biomarkers p16INK4 and ki-67 can assist in the differential diagnosis, confirming the origin of the lesion, but systematic detection is not necessary in clinical practice. For lesions classified as exophytic condyloma acuminata and variants, frequently associated with HPV genotypes 6 and 8, p16INK4 staining is typically weak or patchy, thus differentiating it from high grade VIN. Staining with ki-67 in the middle and upper epithelial layers confirms increased proliferative activity in these strata, a pattern not observed in normal epithelium.

7.4. DIFFERENTIAL DIAGNOSIS

Differential diagnosis is very extensive. This section discusses the most common and most relevant associated entities.
Normal anatomical structures

- **Vestibular papillomatosis**: Digitiform proliferations of the mucosa surrounding a connective-vascular axis. These are located on the inner side of the labia minora, sometimes extending throughout the whole vestibule, and are unrelated with HPV56. It is a benign condition with no pathological correlation.

- **Fordyce spots** are heterotopic sebaceous glands. They present in the form of yellowish white papules 1-3 mm in diameter, isolated or grouped in plaques located particularly in the labia minora and inner side of the labia majora.

Lesions secondary to infections

**Molluscum contagiosum**: lesion of viral etiology (poxvirus), specifically Molluscipoxvirus. It presents as pinkish or skin-coloured papules, with a smooth surface and characteristic central umbilication.

**Benign tumours**:

- **Acrochordon or soft fibroma**: located mainly in the flexures. This is a tumour of dermal etiology, with a pedunculated or sessile implantation base and a smooth surface. No changes from original skin pigmentation are generally seen.

- **Seborrheic keratosis**: this has a verrucous appearance and brown or greyish coloration. Lesions are generally rounded or oval, with a raised, rough surface.

- **Angiokeratomas**: acquired vascular tumours. They present as isolated or multiple, non-coalescent papules, bluish-reddish in colour, measuring 1-5 mm approximately.

- **Hemorrhoidal folds and hemorrhoids**: These are vascular dilations of the hemorrhoidal veins. They present in the form of anal tumours, with a smooth bluish surface, or as skin folds in the perianal area of the same colour as the adjacent skin.

**Malignant tumours**

Malignancy should be suspected in the presence of hard, ulcerative, exophytic lesions, with fleshy borders and bleeding surface.

Special forms

**Giant condylomatosis or Buschke-Löwenstein tumour**: this presents in the form of fast-growing, vegetating, fleshy, exophytic genital lesions. This is a benign tumour, highly capable of causing local destruction, but incapable of becoming malignant or metastatic.

**Bowenoid papulosis**: these are dark brown, brownish gray or black semispherical papular lesions with a shiny surface, that may be isolated or converging, generating plaques of varying sizes. In the vulva, it is considered carcinoma in situ, and may progress to invasive carcinoma. The existence of occult invasive carcinoma must be ruled out, particularly when lesions are extensive and in women of advanced age.

7.5. CONDYLOMATA AS A RISK MARKER OF PRECANCEROUS LESIONS OF THE GENITAL TRACT

There is an association between condyloma acuminata and anogenital cancer. A large, recently published study in 16,155 men and 32,933 women found that individuals with a diagnosis of condyloma acuminata had a higher risk of developing various types of anogenital cancer as well as head and neck cancer. This increased risk was maintained for more than 10 years after the diagnosis of condyloma acuminata.

Although the evidence published to date suggests that condyloma acuminata are markers of precancerous lesions of the genital tract, until more data on this topic are available, women who have or have had condyloma acuminata in the past must undergo screening for cervical cancer in accordance with the Spanish guidelines on cervical cancer screening published in 2014.

7.6. EXTRAGENITAL EXAMINATION (OROPHARYNX AND ANUS)

- **Anus**: Women with condyloma acuminata on the anal rim or those who have symptoms, such as rectal bleeding, irritation or itching should undergo examination of the anal canal by proctoscopy. This
recommendation is independent of whether patients report anal relations or not, since HPV can infect the anal mucosa from the vulva, vagina or even the cervix.

- **Oropharynx**: examination of the oral cavity remains controversial. Some authors recommend that each and every area exposed during sexual relations should be examined. However, a review of the literature does not reveal any clear indication in this respect, nor has any appropriate systematic protocol been described for a definitive examination of either the oral cavity or the oropharynx.

### KEY CONCEPTS

<table>
<thead>
<tr>
<th>Diagnosis of condyloma acuminata is based primarily on physical examination.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lesions must be biopsied if malignant disease need to be ruled out or if treatments are ineffective.</td>
</tr>
<tr>
<td>HPV determination is not recommended for the diagnosis of condylomata.</td>
</tr>
</tbody>
</table>
8. Treatment

8.1. GENERAL PRINCIPLES

The treatment plan for condyloma acuminata must take into account the different options available for treatment and appropriate communication with the patient, so that she can understand: 1) the natural history of the disease, 2) the aim of the treatments, 3) the possible adverse effects, 4) the cure rate, and 5) the chances of relapse.

Multiple options are available for the treatment of condyloma acuminata, ranging from not treating or taking a waiting approach, to the combination of several treatment modalities. There is no scientific evidence that shows any treatment to be clearly superior to others, so treatment must always be individualized, since no single treatment exists that is the most appropriate for all women and for all types of condyloma acuminata. The main variables to take into account when selecting a certain treatment are listed in box1.

<table>
<thead>
<tr>
<th>Box1. Variables to take into account when selecting treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Age.</td>
</tr>
<tr>
<td>• Site, number, area involved, and grade of keratosis.</td>
</tr>
<tr>
<td>• Special situations: pregnancy, childhood, immunosuppressive states.</td>
</tr>
<tr>
<td>• Scientific evidence.</td>
</tr>
<tr>
<td>• Personal experience and preferences of the treating physician.</td>
</tr>
<tr>
<td>• Patient preferences.</td>
</tr>
<tr>
<td>• Possibility of adherence and appropriate follow-up.</td>
</tr>
<tr>
<td>• Efficacy.</td>
</tr>
<tr>
<td>• Persistence and relapse rates.</td>
</tr>
<tr>
<td>• Toxicity, side effects.</td>
</tr>
<tr>
<td>• Availability and price.</td>
</tr>
</tbody>
</table>

Reports of simultaneous or sequential use of different treatments in the literature are scarce, so data on efficacy and complications are limited. The possible combinations of different treatments, and therapeutic sequences, make it very difficult to analyze the published series. Despite the limited evidence, it is advisable in the clinical practice and in certain cases to administer treatments that involve a combination of several options, particularly in cases with poor response or risk of persistence/relapse such as it occurs in immunosuppressed patients.

8.2. CYTOTOXIC AGENTS

8.2.1. Podophyllotoxin

**Mechanism of action**

Prevents cell proliferation by inhibiting mitosis and DNA synthesis.

**Posology**

There are two dosage forms, 1) cream 0.15% (1.5 mg/g; cream 5 g), for self-application, and 2) cutaneous solution 5% (5 mg/ml; 3 ml bottle), that while it can be self-applied, is a potentially more toxic treatment, so its administration should be monitored to ensure appropriate compliance. Podophyllotoxin is applied twice a day for 3 consecutive days, followed by a rest period of 4 days. This schedule is repeated for up to 4 cycles for the cream and 2 cycles for the solution. The cream can be applied with the fingers and the solution with a cotton bud, and both must be applied as selectively as possible to the lesions. Hands should then be washed and contact with the eyes should be avoided.

**Adverse effects**

Cutaneous reactions at the application site and tissue destruction have been described in cases of excessive application (particularly with the solution formulation), and systemic neurological toxicity, particularly if it is applied to ulcerated lesions where there is a possibility of drug absorption.

**Indication**

Treatment of condyloma with limited volume and extension in the external genital, perineal, and perianal areas. Contraindicated during pregnancy and breastfeeding. **Quality of evidence: high; Grade of recommendation: strongly in favour**
Rationale
The efficacy of this treatment, assessed in a meta-analysis, shows complete clearance of lesions in 56% of patients. In other more recent studies, clearance was 72% and relapse rate was up to 79%.

8.2.2. Trichloroacetic acid (TCA)

Mechanism of action
Caustic agent that destroys condylomata by chemical coagulation of proteins and direct damage of viral DNA.

Posology
Prepared using a magistral formula (concentration 80%-90%) and applied in the doctor’s office by a healthcare professional. Application must be selective to the lesion with a swab previously soaked in the solution. It must not be applied to the healthy skin surrounding the lesion, so it is useful to protect the borders of the lesion with a Vaseline barrier. After application, let the solution dry in the air until it achieves a whitish appearance. Changes in position must be avoided during treatment to prevent the product spreading due to its low viscosity.

The dosage schedule is weekly, up to a maximum of 10-12 weeks. Most lesions clear between 4 and 6 weeks.

Adverse effects
The most common and immediate adverse effect is pain in the area of application as a sign of overexposure to the product. If this occurs, the area can be washed with a solution of bicarbonate of soda. In cases of extreme overexposure, ulcers, erosions and burns may occur.

Indication
Treatment of condyloma with limited volume and extension on external genitalia or mucosa (anogenital). Quality of evidence: high; Grade of recommendation: strongly in favour

Rationale
Efficacy evaluated in various studies shows complete lesion clearance in 56%-81% cases, with a relapse rate of 36%.

8.3. IMMUNOMODULATORS

8.3.1. Imiquimod

Mechanism of action
An immune-modulating drug that increases local immune response mediated by interferon and other cytokines.

Posology
- Application of 5% cream 3 times a week on non-consecutive days (e.g., Monday, Wednesday and Friday) for up to 16 weeks.
- Application of 3.75% cream once a day for up to 8 weeks. Currently in Spain, the dosing form of 3.75% cream is only approved for the treatment of actinic keratosis.

The cream is self-applied by the patient, normally at night, and it is advisable to wash the area with soap and water 6-10 hours after application. The patient should wash her hands before and after each application.

Adverse effects
The main side effect is inflammation and local erythema, normally mild or moderate, although exceptional cases of erosions and sequelae such as post-inflammatory hypopigmentation and scleroatrophic lichen have been described. Local reactions can be reduced by introducing rest periods, or reducing the frequency of application. Although systemic absorption is minimal, headache, asthenia, myalgias, and nausea may occur. The use of imiquimod has been associated with a worsening of inflammatory and autoimmune diseases, such as psoriasis, vitiligo, or lupus, or the appearance of distant reactions such as erythema multiforme or Steven-Johnson syndrome.

Indication
Treatment of condyloma on external genital, perineal and perianal areas. Insufficient data are available to recommend this treatment in women during pregnancy or breastfeeding, however, studies in animals have shown no toxic effects. Quality of evidence: high; Grade of recommendation: strongly in favour.
Rationale

Efficacy assessed in studies shows a response rate of 72%-84% (complete response in 40%-70%). 5% cream is usually effective after 8-10 weeks (50% complete clearance within 12 weeks). Patient whose lesions are not completely cleared show a significant reduction in lesion size. The relapse rate ranges from 13% to 19%52,62,71,73-77.

8.3.2. Sinecatechins (Polyphenon E)

Mechanism of action

Sinecatechins are derived from an extract of green tea leaves (Camellia sinensis). Epigallocatechin gallate is the most important catechin. It can intervene in multiple cell signalling pathways, inhibiting the cell cycle, activating the apoptosis of virus-infected cells and inhibiting HPV transcription78,79. It has antioxidant and antiviral activity, and strengthens the immunological system.

Posology

The marketed dosage form in Spain is a 15 g tube of 10% ointment (in other countries, such as the U.S., it is sold at 15%). It is applied 3 times a day, using the fingertip to distribute a fine layer of ointment over the area to be treated. The area must not be subsequently washed. The treatment is applied until the lesions have completely cleared, up to a maximum of 16 weeks..

Adverse effects

Adverse effects occur in up to 80% of cases. In general, adverse effects such as erythema and erosion are local and correlate with lesion clearance. They usually appear at the end of week 3, and intensify after week 4-6. The patient must be informed that these adverse events correlate with the beginning of lesion clearance. Exceptionally, sequelae, such as changes in pigmentation and stenosis of the urethral meatus, have been described81,82.

Indication

Treatment of condyloma on external, perineal, and perianal genitalia. Insufficient data are available to recommend this treatment in women during pregnancy or breastfeeding. Quality of evidence: high; Grade of recommendation: strongly in favour.

Rationale

Efficacy assessed in 2 trials shows a clearance rate of prevalent and incidental condyloma acuminata of 47%-59% (in patients completing the 16-week treatment course, complete clearance was 64.5%), and relapse rates ranging between 7%-11% (after a follow-up of 12 weeks)80,83,84.

8.4. EXCISION

It consists of the total excision of the lesion with a cold scalpel or electro surgical procedures (electric scalpel or diathermic needle). Careful hemostasis must be applied to the surgical bed, without cauterization extending to the subcutaneous or submucosal fat, which can cause unaesthetic or painful scars, or stenosis. This procedure requires anaesthesia (local, regional or general) and involves the usual surgical risks, such as infection and bleeding.

The advantage of surgical intervention is that it provides immediate results, particularly in patients with large, obstructive or extensive condylomata.

Indication

This is not the treatment of choice for anogenital condyoma. Its use may be justified in the following cases: 1) failure of previous treatments, 2) unavailability of other treatments, 3) large volume of condyloma requiring combined treatment, 4) suspicion of infraepithelial or invasive neoplasm requiring histological study of lesions. Quality of evidence: low; Grade of recommendation: strongly in favour.

Rationale

A recent revision reported an efficacy rate of 89%-100% and a relapse rate of 19%-29%, 10-12 months after completing treatment82.
8.5. ABLATION

8.5.1. Cryotherapy

**Mechanism of action**

Cryotherapy uses low-temperature liquid nitrogen (-196°C) to destroy tissues, causing epidermal and dermal necrosis.

**Technique**

Cryotherapy consists of the application of liquid nitrogen to the lesion, either pulverized or with a previously soaked cotton bud. Another option is applying nitric oxide or carbon dioxide to the lesion, using a cryoprobe. It is usually applied once a week, with 2-3 freeze-thaw sequences per session. Treatment is repeated every 2-3 weeks for up to 3-4 months.

**Adverse effects**

Blisters can appear after treatment, but they re-epithelize in a few days. Sequelae such as scars or pigment changes are rare.

**Indication**

Treatment of condyloma acuminata in any area of the anogenital tract. 

**Quality of evidence:** high; Grade of recommendation: strongly in favour.

**Rationale**

Efficacy assessed in several studies shows complete clearance of lesions in 44%-75% of patients\(^{85-88}\) and in most cases, this occurs in around the third session. However, as cryotherapy has no antiviral activity and does not modulate the immune system, relapse rates are high, from 21% to 42% after a follow-up period of 1-3 months\(^{97}\). The effect of combining cryotherapy followed 1 week later by sinecatechins (sequential treatment) has been studied and shows better results than cryotherapy alone\(^{89}\).

8.5.2. Láser CO2

**Mechanism of action**

The physical basis of CO2 laser is that energy applied to the water in the tissues in the form of a laser beam is absorbed, causing the water to boil, thus vaporizing the tissue.

**Technique**

Colposcopic monitoring must be used to monitor this technique in the operating room or outpatient surgical centre. Regional anaesthesia or sedation is required, and prior specialized training is essential. The effects of the laser and the depth of tissue penetration vary depending on the power applied, the size of the focal point used on the tissue, and the time of application. It is best not to apply the laser at a depth of more than 1 mm to avoid sequelae from scarring. Protective masks and fume extractors must be used. The infectious nature of vaporized viral fragments contained in the smoke has not been proven, but any problems from inhalation can be reduced as far as possible with the use of these measures\(^{90,91}\).

**Adverse effects**

Adverse effects are generally mild and include scarring and pain.

**Indication**

Treatment of condyloma in any area of the anogenital tract.

**Quality of evidence:** low; Grade of recommendation: weakly in favour.

**Rationale**

This technique is effective, with a very high rate of elimination of warts (all visible lesions can often be vaporized); however, relapse rates are high, but the data in the literature vary widely, since these series contain cases that are refractory to other treatments or high-risk patients (recurrences of 12.6 % at 1 month, up to 77%)\(^{92,94}\).

8.5.3. Diathermy electrocoagulation

This is similar to traditional electrocoagulation, but causes less subdermal damage. The scalpel point or a diathermic ball may be used. Prior local anaesthesia is required. A fine-point diathermy scalpel can also be used for excision.

**Indication**

Treatment of condyloma limited in number and extension in any area of the anogenital tract. This technique is not suitable for multiple lesions or large disease volume. 

**Quality of evidence:** high; Grade of recommendation: strongly in favour.
Rationale
A recent review reported an efficacy rate of 94%-100% and a relapse rate of 22%, 3 months after completing treatment\textsuperscript{52}.

8.6. OTHER INVESTIGATIONAL TREATMENTS

8.6.1. Photodynamic Therapy (PDT)

Mechanism of action
The therapeutic effect of PDT in condyloma acuminata is due to the activation of the dendritic cells and CD4 lymphocytes in lesional skin\textsuperscript{95}.

Technique
Prior application of a photosensitizer (5-aminolevulinic acid or ALA), which accumulates in the HPV infected cells, that will then be destroyed by photo-oxidation.

Adverse effects
The main adverse effect is pain. Cases of erythema, erosions and ulcers have been described.

Indication
Its use should currently be limited to the scope of investigational studies of condyloma in any area of the genital tract.

Rationale
A few studies suggest that 1 or 2 sessions of PDT with ALA might be as effective as surgery or laser, with lower relapse rates at 12 weeks\textsuperscript{96,97}. The available evidence is insufficient to propose PDT as first-line treatment for warts of the anogenital area, but it may have a role in refractory cases, or when it is desirable to preserve functional anatomy. The combination of PDT with cryotherapy has been proposed, in view of PDT activity in subclinical lesions, and better results have been reported than with cryotherapy alone\textsuperscript{98}. Quality of evidence: not applicable; Grade of recommendation: not applicable.

8.6.2. Cidofovir

Mechanism of action
This deoxycytidine monophosphate nucleotide analogue acts by inducing apoptosis of HPV-infected cells. It reduces E6 and E7 expression, permitting the expression of suppressor proteins p53 and pRb in vitro\textsuperscript{99,101}.

Posology
Topical formulation (gel, cream or intralesional) at 1% or 3%, applied 1 or 2 times a day, up to a maximum of 10 weeks. This indication does not appear in the product labelling.

Adverse effects
Topical administration in a cream or intralesionally is safe, particularly if it is used on non-ulcerated skin or mucosa, although its intravenous use is associated with systemic toxicity (nephrotoxicity, neutropenia, metabolic acidosis, and ocular toxicity), and application must be strictly monitored.

Indication
Second-line treatment of condylomata in any area of the anogenital tract (not listed in product labelling). This may be a resource to take into account in immunocompromised patients with hard-to-treat condylomata refractory to other therapies.

Rationale
Two randomized, controlled clinical trials have been performed evaluating the efficacy of cidofovir compared to placebo in the treatment of anogenital condylomata. In both studies, cidofovir was significantly superior to placebo. In the Snoeck trial, 47% of patients achieved complete remission, with a good safety profile\textsuperscript{102}. The regimen was: cidofovir gel 1% for 5 consecutive days in alternate weeks for up to 6 weeks, depending on progress. The trial of Matteelli in HIV-infected patients showed a more than 50% reduction in lesions in 58% of patients after treatment with cidofovir cream 1%, 5 days a week for 2 weeks followed by 2 weeks of observation\textsuperscript{103}. Quality of evidence: not applicable; Grade of recommendation: not applicable.
8.7. QUALITY OF EVIDENCE AND RECOMMENDATIONS FOR TREATMENTS COMMONLY USED IN NON-PREGNANT IMMUNOCOMPETENT WOMEN ACCORDING TO THE GRADE SYSTEM

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Grade of recommendation</th>
<th>Quality of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Podophyllotoxin</td>
<td>Strongly in favour</td>
<td>High</td>
</tr>
<tr>
<td>Trichloroacetic acid</td>
<td>Strongly in favour</td>
<td>High</td>
</tr>
<tr>
<td>Imiquimod</td>
<td>Strongly in favour</td>
<td>High</td>
</tr>
<tr>
<td>Sinecatechins (Polyphenon E)</td>
<td>Strongly in favour</td>
<td>High</td>
</tr>
<tr>
<td>Excision</td>
<td>Strongly in favour</td>
<td>Low</td>
</tr>
<tr>
<td>Cryotherapy</td>
<td>Strongly in favour</td>
<td>High</td>
</tr>
<tr>
<td>CO2 laser</td>
<td>Weakly in favour</td>
<td>Baja</td>
</tr>
<tr>
<td>Diathermy electrocoagulation</td>
<td>Strongly in favour</td>
<td>High</td>
</tr>
<tr>
<td>Photodynamic therapy</td>
<td>Not applicable</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Cidofovir</td>
<td>Not applicable</td>
<td>Not applicable</td>
</tr>
</tbody>
</table>

Table 3. Treatment of condyloma acuminata in pregnant women

<table>
<thead>
<tr>
<th>Treatment</th>
<th>AUTHORIZED</th>
<th>REASON</th>
</tr>
</thead>
<tbody>
<tr>
<td>Podophyllotoxin</td>
<td>No</td>
<td>Teratogenic</td>
</tr>
<tr>
<td>Sinecatechins</td>
<td>No</td>
<td>Sparse data</td>
</tr>
<tr>
<td>Imiquimod</td>
<td>No</td>
<td>Sparse data</td>
</tr>
<tr>
<td>CO2 laser</td>
<td>YES*</td>
<td>Safe</td>
</tr>
<tr>
<td>Cryotherapy</td>
<td>YES*</td>
<td>Safe</td>
</tr>
<tr>
<td>TCA</td>
<td>YES*</td>
<td>Safe</td>
</tr>
<tr>
<td>Excision</td>
<td>YES*</td>
<td>Safe</td>
</tr>
<tr>
<td>Diathermy electrocoagulation</td>
<td>YES*</td>
<td>Safe</td>
</tr>
</tbody>
</table>

*Including vaginocervical and anal mucosa

8.8. TREATMENT UNDER SPECIAL CIRCUMSTANCES

8.8.1. Pregnancy

In general, treatment is preferred to a waiting approach. In some cases, condyloma growth during pregnancy can be remarkable. The aim of treatment is to reduce the viral load, reduce perinatal exposure, and avoid lesion growth and proliferation, which, in cases of large protruding lesions, can make vaginal delivery difficult or impossible.

The main medical options are contraindicated. Podophyllotoxin has been shown to be embryotoxic. Little data is available on the safety of imiquimod and sinecatechins in pregnancy.

Recommended options are summarized in Table 3.

8.8.2. Immunosuppression

Condyloma acuminata in immunosuppressed women are more common and larger in size, occur in uncommon sites, are resistant to treatment, and tend to relapse.

Therapies that activate the immune system (imiquimod and sinecatechins) may be less effective. Several studies show the efficacy of imiquimod in these patients. Trichloroacetic acid and ablative treatments, such as cryotherapy and CO2 laser, are effective in these patients. Excisional therapy is indicated in all cases that require a histological study to rule out neoplastic lesions associated with condyloma (more common in this population).

On occasions, the severity and refractoriness of lesions require sequential or combined use of multiple treatments or more experimental treatments, such as cidofovir. Moreover, re-establishing a normal immune status (with antiretroviral treatment) is of inestimable help in controlling this disease. A waiting approach may be taken in cases of apparently reversible immunosuppression, since lesions have been seen to resolve after recovery of normal immunological parameters (CD4, viral load).
8.8.3. Childhood

Due to high rates of spontaneous resolution, a waiting approach can be taken initially. The safety of medical treatments in childhood has not been proven, so they are inadvisable; most authors opt for ablative procedures, such as CO2 laser.

8.9. TREATMENT OF CONDYLOMATA IN OTHER AREAS OF THE GENITAL TRACT

8.9.1. Vagina

Vaginal condylomata are generally multifocal, extensive lesions. Treatments of choice are ablative treatments such as cryotherapy, CO2 laser vaporization, and diathermic electrocoagulation, or cytotoxic treatments such as trichloroacetic acid.

Podophyllotoxin is contraindicated due to the risk of systemic absorption. Immunomodulators such as imiquimod and sinecatechins are not recommended, due both to the risk of severe mucositis, and possible systemic absorption.

8.9.2. Cervix

Condyloma acuminata on the cervix requires a colposcopy to be performed before a therapeutic decision can be reached. Cases without SIL can be treated with CO2 laser, cryotherapy, electrosurgery, or trichloroacetic acid. Podophyllotoxin, imiquimod and sinecatechins are not recommended for the same reasons discussed above.

8.9.3. Anus

In intra-anal condyloma acuminata, the treatment of choice is ablative. The use of trichloroacetic acid or cryotherapy can be considered in small, sparse lesions. The treatment of choice when involvement is extensive is surgery, using electrocoagulation, CO2 laser, or infrared coagulation.

While its use is not approved in mucosa, imiquimod cream or suppositories has been used in case series and clinical trials in coadjuvancy with surgery in cases of extensive intra-anal warts; results have been promising (Table 4).

| Tratamiento de condilomas acuminados en mucosas vaginocervical y anal |
|---------------------------------|-----------------|
| **AUTORIZADO**                  | **RIESGOS**     |
| Imiquimod*                     | No              |
| Podofilotoxina                 | No              |
| Sinecatequinas                 | No              |
| Láser CO2                      | SI              |
| Crioterapia                    | SI              |
| ATCA                           | SI              |
| Escisión                       | SI              |
| Electrocoagulación diatémica   | SI              |

* en algunas series, imiquimod se ha probado en mucosas en preparaciones en crema o supositorios 115-118
8.10. TREATMENT ALGORITHM

Condyloma acuminata treatment algorithm (adapted from ref. 119).

### KEY CONCEPTS

There is no scientific evidence that shows any treatment to be clearly superior to others.

Treatment must always be individualized, since no single treatment exists that is most appropriate for all women and for all types of condyloma acuminata.

In pregnant patients, the preferred options are cryotherapy, CO2 laser, and trichloroacetic acid.

In immunosuppressed patients, therapies that activate the immune system may be less effective. For this reason, the preferred options are cryotherapy, CO2 laser, and trichloroacetic acid.
9. Post-treatment follow-up

The aim of post-treatment follow-up is to confirm cure and/or diagnose relapse of lesions\textsuperscript{120,124}.

**Follow-up schedule**

After lesion clearance, follow-up visits should be performed at 3, 6 and 12 months. If, after this time, the patient remains lesion-free, specific follow-up for condyloma acuminata is not required, but screening tests for cervical cancer should be performed as appropriate.

**Rationale**

The overall relapse rate, including new lesions in previously treated or untreated sites, is generally 20\%-30\%. Post-treatment relapse of condyloma acuminata is considered if new lesions appear within the first 6 months of follow-up. Most relapses occur between 3 and 6 months after the end of treatment\textsuperscript{52}. This means that after lesions are resolved, the patient must be informed that it is not uncommon for new lesions to occur within 3-6 months after clearance\textsuperscript{120,123-125}. After 1-2 years, HPV presence falls to undetectable levels, so the risk of relapse reduces.

Relapsing condylomata must be treated again with the initial treatments that were found to be effective, without forgetting to take into account other treatments, depending on the extension and the site of the lesions. An examination of the patient’s partner is not required\textsuperscript{123}.

### KEY CONCEPTS

The appearance of condyloma acuminata in the first 6 months after resolution is considered as relapse.

In these cases of relapse, the treatment to be used should be the same as the initially selected treatment, according to the most appropriate therapeutic strategy.
The most effective prevention for the appearance of condyloma acuminata is HPV vaccination, particularly if this is given before exposure to the viruses included in the vaccine.

Three prophylactic anti-HPV vaccines are currently available. The 2 vaccines which include the HPV genotypes associated with condyloma acuminata and which are indicated in the product labelling for the prophylaxis of these strains are: Gardasil® (tetravalent vaccine) and Gardasil9® (recently introduced nonavalent vaccine). The third, Cervarix® (bivalent vaccine), does not include the HPV genotypes involved in the genesis of condyloma acuminata. However, some discrete effectiveness of this vaccine in the reduction of condyloma has recently been reported among women in the United Kingdom between 2008 and 2011. This issue is currently being investigated and discussed.

Most studies that support the effectiveness of the HPV vaccine in the prevention of condyloma acuminata have been performed in women who received the Gardasil® vaccine. A large study performed in the whole population of Sweden showed that the vaccine was effective in the prevention of condylomata in 93% of the younger cohorts (< 14 years). The vaccine was less effective in older cohorts, suggesting that the maximum effect was in girls not previously exposed to HPV. An Australian study showed a 92.6% reduction in the incidence of condyloma acuminata in the female population under 21 years of age, 4 years after the start of a systematic vaccination campaign with Gardasil®. In this study, none of the 235 women under 21 years of age was diagnosed with condylomata (Figure 2).

This same study found a reduction in condyloma acuminata in the heterosexual male population under the age of 30 years (Figure 3), due to the herd immunity effect, while there was no impact on individuals over the age of 30 among the homosexual population (Figure 4).
In 2015, a systematic review of 354 articles, of which 56 were selected and analyzed, was published. Of these, 16 provided data on the impact and effectiveness of the tetravalent vaccine on condylomata in 6 countries (Australia, New Zealand, USA, Denmark, Germany, and Sweden), which showed that, despite the different study designs, study populations, and vaccine implementation and cover, the incidence of condylomata fell rapidly after the introduction of the tetravalent vaccine, at least in the target population. Moreover, rates of other sexually transmitted disease increased or remained stable, suggesting that the reduction in the incidence of condyloma acuminata is not explained by changes in sexual education or habits\(^{128}\).

Another systematic review, also published in 2015, which included 20 studies performed in 9 developed countries, showed that in countries where at least 50% females are vaccinated (tetravalent vaccine), the rate of anogenital condylomata falls significantly, not only in girls aged 16-19 years (61% [0.39, 0.22-0.71]), but also in males under the age of 20 (0.66 [95% CI 0.47-0.91]) and in women aged 20-39 years (0.68 [95% CI 0.51-0.89]), suggesting a herd immunity effect. In contrast, when female vaccination cover is less than 50%, the cases of anogenital condylomata falls (0.86 [95% CI 0.79-0.94]) in females younger than 20 years of age, but no crossover protection or herd immunity is observed (Figure 5)\(^{129}\).

Despite their limitations, these studies show that vaccination programs with tetravalent vaccines have the potential to significantly reduce the burden associated with condyloma acuminata. Some models based on data extracted from clinical trials and estimates on the high burden of costs to healthcare systems associated with condylomata, predict that the costs of vaccination may be compensated by the reduction in the costs associated with the treatment and follow-up of this disease.

A cohort study in 100,000 women conducted in Holland estimated that the tetravalent vaccine would also prevent 4,930 cases of condylomata, which would reduce the incremental cost-effectiveness ratio (ICER) to 16,300 euros/QALY (quality-adjusted life-year)\(^{130}\).

**KEY CONCEPTS**

Nowadays, a very effective primary prevention of condyloma acuminata is possible.

Vaccination with vaccines that contain viral genotypes 6 and 11 (tetravalent and nonavalent) are nowadays the most effective method for the primary prevention of condyloma acuminata, and these vaccines are maximally effective if administered before the beginning of sexual relations.
Figure 5. Changes in the diagnosis of condyloma acuminata between the pre-vaccination and post-vaccination period in (A) girls aged 15-19 years, (B) women 20-39 years, (C) boys aged 15-19 years, and (D) men 20-39 years, associated with the rate of vaccine cover among the female population.
11. Recommendations

1. Women who have or who have had condyloma acuminata in the past should undergo cervical cancer screening in accordance with the cervical cancer screening guidelines for Spain published in 2014.

2. The use of acetic acid in the vulva, vagina and/or cervix to reveal smaller condyloma acuminata is not recommended as it can lead to false positive diagnoses.

3. If condyloma acuminata are detected in the anovulvar area, the vagina and the cervix should be examined.

4. Biopsies should be obtained if precancerous or cancerous disease is suspected or if lesions worsen during treatment.

5. HPV determination is not indicated in patients with condyloma acuminata, since this does not add clinical information nor does it modify the approach to such lesions. It may be indicated in the paediatric population only, since it is often necessary to rule out or confirm the existence of HPV, due to the possible association between HPV infection and sexual abuse of the minor.

6. Women with condyloma acuminata on the anal rim or those who have symptoms such as rectal bleeding, irritation or itching should undergo examination of the anal canal by proctoscopy.

7. Treatment of condyloma acuminata must always be individualized, since no single treatment exists that is the most appropriate for all women and for all types of condyloma acuminata. The main variables to take into account when selecting a certain treatment are:
   - Age.
   - Site, number, area involved, and grade of keratosis.
   - Special situations: pregnancy, childhood, immunosuppressive states.
   - Scientific evidence.
   - Personal experience and preferences of the treating physician.
   - Patient preferences.
   - Possibility of adherence and appropriate follow-up.
   - Efficacy.
   - Persistence rate and relapses.
   - Toxicity, side effects.
   - Availability and price.

8. In the case of condyloma acuminata in pregnancy, the use of podophyllotoxin (embryotoxicity has been proven) and imiquimod and sinecatechins (very few data are available on their safety in pregnancy) should be avoided.

9. Cesarean section is not indicated to terminate gestation in a woman with genital condylomatosi, unless the birth canal is obstructed by lesions or vaginal delivery might cause excessive bleeding.

10. If condyloma acuminata occur in the vaginocervical and/or anal mucosa, the use of podophyllotoxin, imiquimod, and sinecatechins should be avoided due to the risk of severe mucositis and possible systemic absorption of these drugs.

11. In the case of condyloma acuminata in childhood, due to high rates of spontaneous resolution, a waiting approach can be taken initially.

12. The use of medical treatment of condyloma acuminata in childhood is not recommended, as the safety of these products has not been proven.

13. If condyloma acuminata is detected in childhood, the possibility of sexual abuse should be ruled out.

14. After clearance of condyloma acuminata, follow-up visits should be performed at 3, 6 and 12 months for the detection of relapse.

15. Relapsing condyloma must be treated again with the initial treatments that were found to be effective.

16. The most effective prevention for the appearance of condyloma acuminata is HPV vaccination, particularly if this is given before exposure to the viruses included in the vaccine.
12. References


35


Condyloma acuminata