CONSENSUS
DOCUMENT

DIAGNOSIS AND TREATMENT OF SEXUALLY TRANSMITTED INFECTIONS IN ADULTS, CHILDREN AND ADOLESCENTS

GOBIERNO DE ESPAÑA
MINISTERIO DE SANIDAD
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GEITS
GRUPO DE ESTUDIO EN INFECCIONES DE TRANSMISIÓN SEXUAL

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ABBREVIATIONS

AC: Autonomous Communities.

AEEH: Spanish Association for the Study of the Liver.

AIDS: Acquired immunodeficiency syndrome.

ALP: Alkaline phosphatase.

ALT: Alanine aminotransferase.

Anti-HAV: HAV antibodies.

Anti-HBc: Antibody against hepatitis B core

Anti-HBe: Antibody against hepatitis B 'e'

Anti-HBs: Antibody against hepatitis B

Anti-HCV: HCV antibodies antigen.

Anti-HDV: HDV antibodies antigen.

Anti-HEV: HEV antibodies antigen.

APC: Annual Percent Change.

APRI: AST to Platelet Ratio Index.

AS: Anal sex.

ASC-H: Atypical squamous cells not excluding high grade.

ASC-US: Atypical squamous cells of undetermined significance.

AST: Aspartate aminotransferase.

BLV: Bulevirtide.

cccDNA: Covalently closed circular DNA.

CDC: Centers for Disease Control and Prevention.

CLIA: Chemiluminescent microparticle immunoassay.

CMV: Cytomegalovirus.

CoC: Chain of custody

CSE: Comprehensive sex education.

CT: *Chlamydia trachomatis*.

DAA: Direct acting antiviral agents.

DNA: Deoxyribonucleic acid.

DOT: Directly observed therapy.

Doxy-PEP: Doxycycline post-exposure prophylaxis.

EC-IVD EC: EC certificate for in vitro diagnostic medical devices.

ECDC: European Centre for Disease Prevention and Control.

EIA: Enzyme immunoassay.

EMA: European Medicines Agency.

FDA: Food and Drug Administration.

FIB-4: Fibrosis indicator based on age, ALT, AST and platelets.

FMU: First morning urine.

FTC: Emtricitabine.

GBMSM: Gays, bisexuals and other men who have sex with men.

GEHEP: Study Group for Viral Hepatitis.

GeSIDA: Study Group for AIDS.

GGT: Gamma glutamyl transferase.

GLE: Glecaprevir.

GNB: Gram-negative bacillus.

GU: Gonococcal urethritis.

GV: Gardnerella vaginalis.

HAV: Hepatitis A virus.

HBcAb: Antibodies to HBV core.

HBsAg: Hepatitis B surface antigen.

HBV-DNA: Hepatitis B virus DNA.

HBV: Hepatitis B virus.

HCC: Hepatocellular carcinoma.

HCV: Hepatitis C virus.

HDV: Hepatitis D virus.

HEV: Hepatitis E virus.

HIV: Human immunodeficiency virus.

HPV: Human papillomavirus.

HR: High risk.

HRA: High-resolution anoscopy.

HSIL: High-grade squamous intraepithelial lesion.

HSV: Herpes simplex virus.

HT: Healing test.

IDU: Intravenous drug users.

IM: Intramuscular.

IQR: Interquartile range.

IV: Intravenous.

kPa: Kilopascals.

LGV: Lymphogranuloma venereum.

LSIL: Low-grade squamous intraepithelial lesion.

MG: *Mycoplasma genitalium*.

MO: Microorganism.

Mpox: Infection with simian smallpox virus.

MSM: Men who have sex with men.

MSW: Men who have sex with women.

MU: Millions of units.

NAAT: Nucleic acid amplification technique.

NG: Neisseria gonorrhoeae.

NGO: Non-governmental organisation.

NGU: Nongonococcal urethritis.

NILM: Negative for intraepithelial lesion or malignancy.

NTCP: Na+-taurocholate cotransporting polypeptide.

OAS: Oro-anal sex.

OS: Oral sex.

PCR: Polymerase chain reaction.

PEG-INF: Pegylated interferon-alpha 2a

PEG-INF: Pegylated interferon.

PEP: Post-exposure prophylaxis.

PEP: Post-exposure prophylaxis.

PGB: Penicillin G benzathine.

PHIV: People with HIV.

PIB: Pibrentasvir.

PID: Pelvic inflammatory disease.

PLHIV: People living with HIV.

PMN: Polymorphonuclear.

PO: Oral use.

PO: Oral use.

POC: Point of care.

PrEP: HIV pre-exposure prophylaxis.

PWID: People who inject drugs.

qHBsAg: Quantitative HBV surface antigen.

RAHC: Recently acquired Hepatitis C

RBV: Ribavirin.

RHT: Rapid HIV testing.

RNA: Ribonucleic acid.

SD: Single dose.

SD: Single dose.

SOF: Sofosbuvir.

STI: Sexually transmitted infections.

surface antigen.

SVR: Sustained virologic response.

TAF: Tenofovir alafenamide fumarate.

TDF: Tenofovir disoproxil fumarate.

TMA: Transcription-mediated amplification.

TP: *Treponema pallidum*.

TSH: Thyroid-stimulating hormone.

TV: *Trichomonas vaginalis*.

TW: Transgender woman.

UNAIDS: Joint United Nations Programme on HIV/AIDS.

VCTE: Vibration-controlled transient hepatic elastography

VEL: Velpatasvir.

VOX: Voxilaprevir.

WHO: World Health Organisation.

CHAPTER 1

INTRODUCTION

1. INTRODUCTION

Sexually transmitted infections (STIs) are mostly contracted through sexual contact, with more than thirty different causative agents, including bacteria, viruses and parasites, having been described.

Their high morbidity and potential for medium and long-term sequelae consume significant health and human resources, as the socio-economic costs of these infections are among the top ten reasons for consultation.

For this reason, tackling these infections is a challenge that has attracted the interest of various international organisations, which have set up global strategies and plans to support countries in this major challenge.[1]

Health professionals play a critical role in their diagnosis, prevention and treatment and should have basic but sufficient knowledge for the correct management of these diseases, both in their approach, contact tracing and follow-up.

The 2024 update of the "Consensus Document on the Diagnosis and Treatment of Sexually Transmitted Infections in Adults, Children and Adolescents" represents a significant advance in clinical care in our country. This achievement is the result of collaboration between various scientific partnerships and associations, nursing and community professionals, which ensures a multidisciplinary approach supported by best practices. One of the most important aspects to highlight is that these guidelines have been developed jointly with the Ministry of Health, through the collaboration agreement signed with the Spanish Society of Infectious Diseases and Clinical Microbiology (SEIMC) [2]and channelled through the Division of HIV, STI, Viral Hepatitis and Tuberculosis Control of the Ministry of Health, which means that these guidelines aim to become the national reference document for the management of STIs in our population.

One of the main innovations of this edition is the unification of all microbiological procedures within each chapter. As a result, there is no need to consult additional documents, thus facilitating access to complete information on clinical and microbiological management in a single resource. The revision of the chapters has always been collaborative and included the participation of a microbiologist, which has further enriched the content. Another important advance has been the prioritization of the etiological approach over syndromic management, although the latter is maintained for its applicability in various contexts, such as primary care, emergencies and other situations where molecular diagnosis is not available on an exceptional basis. In this edition, the cross-cutting integration of the paediatric perspective in each chapter has been an innovative aspect, ensuring that the particularities of this population are taken into account. In addition, a separate chapter has been added to specifically address the needs of this group. Likewise, each corresponding chapter highlights the

specificities in the management, diagnosis and treatment of pregnant women. All these factors contribute to the consolidation of a comprehensive and multidisciplinary guide.

To enhance the reader's experience and optimise learning, an innovative approach has been incorporated: each chapter starts with key messages that outline the most important aspects of each chapter. This structure allows the reader to quickly access the essential information, providing an agile and efficient understanding of the most relevant topics.

The creation and independent updating of new chapters has been fundamental, with chapters on anogenital ulcers, vulvovaginitis, proctocolitis, diseases with cutaneous manifestations (ranging from non-infectious pathologies to emerging infections such as mpox). The addition and revision of the hepatitis chapter were carried out in accordance with the recommendations of the Study Group on Viral Hepatitis (GeHEP) of the SEIMC [Spanish Society of Infectious Diseases and Clinical Microbiology]. The new chapter on sexual assault includes a glossary of legal terms and guidelines for medico-legal management, as well as recommendations for antiretroviral treatment, in line with those of the Study Group for AIDS (GeSIDA) of SEIMC. The updated chapter on human papillomavirus is particularly relevant, with the addition of recommendations for screening for anal dysplasia in various populations according to the latest available evidence. Finally, the inclusion of a chapter dedicated to the Third Sector's approach to STIs will allow the reader to understand the important role played by community organisations in the prevention and control of STIs in our country.

Purpose

The purpose of this document is to inform health professionals of the current situation and to offer tools for the proper management of STIs, which, due to their relevance, need greater attention, both in the general population and in special populations.

This document updates the "Consensus document on the diagnosis and treatment of sexually transmitted infections in adults, children and adolescents" published in March 2017 by the National AIDS Plan (PNS), the Study Group for STI (GeITS) and the Study Group for AIDS (GeSIDA). These recommendations should be regarded as a source of clinical guidance and should always take into account the clinical circumstances of the individual and the context in which they develop.

The drafting panel of the document is composed of experienced STI clinicians appointed by the coordinators and board members of the SEIMC Study Group for STI (GeITS), who have agreed to participate voluntarily and to issue a conflict of interest statement. These experts have been divided into groups of editors and reviewers who have been responsible for updating a section of the document. Three members of the Panel have acted as coordinators and their task has been to bring all the sections of the document together and to prepare and edit the final version of the document. The editors of each group have reviewed the most relevant data from the most recent scientific publica-

tions (PubMed and Embase; languages: English and Spanish) and conference papers up to December 2023. The text produced by the drafter has been submitted to the reviewers for consideration and the contributions accepted by consensus have been incorporated. Once all sections have been assembled, the document has been further discussed and agreed at a Panel meeting. Following the addition of the modifications approved at this meeting, the document is posted for 15 days on the SEIMC website so that professionals, patients or anyone interested can make suggestions which, after study and deliberation, can be included in the final document, in accordance with the SEIMC rules for the publication of scientific documents. The Panel considers that should new relevant evidence leading to changes emerge, it will be incorporated into the document on the web pages and, if possible, in the publication.

The recommendations in these guidelines are based on scientific evidence and expert opinion. Each recommendation is rated with a letter indicating its strength [A (should always be offered), B (should generally be offered) or C (should optionally be offered)] and a number expressing the evidence supporting the recommendation [I (results obtained from one or more randomised clinical trials of clinical or laboratory aspects or a meta-analysis); II (from one or more non-randomised trials or observational cohort data); and III (expert opinion)].

GeITS, the Division of HIV, STI, Viral Hepatitis and Tuberculosis Control of the Ministry of Health and GeSIDA, together with other SEIMC working groups, will continue to update this document periodically in the light of evolving knowledge. However, it is also worth recalling that, as changes occur very rapidly, readers should also consult other sources of information.

We believe that, thanks to the collaboration and combined work between scientific societies, civil society and public administration, we have established this update of our guidelines as a national and international benchmark due to its multidisciplinary nature. In addition, this guide maintains a focus on sexual rights, equity, universal access and respect for gender identity, contributing to the reduction of social inequalities, the humanisation of care and the reduction of morbidity and mortality, and helping to eliminate the stigma associated with sexually transmitted infections.

The coordinators of this guide would like to express their deepest gratitude to all contributors, as well as to the various study groups, societies and scientific associations that have made this consensus document possible. Their time and effort are priceless.

Mar Vera, Javier Gómez, César Sotomayor

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CHAPTER 2

GENERAL STIs PREVENTION AND CONTROL MEASURES

2. General STIs prevention and control measures

KEY MESSAGES

1. A comprehensive anamnesis based on clear, respectful and non-judgemental questions in a trusting environment is key to estimating the risk of exposure to STIs and being able to correctly address STIs.

2. The comprehensive anamnesis should be based on 5 specific aspectssuch as: current medical history, previous history of STIs, sexual practices and behaviours, STI/HIV protective measures, and the possibility to ask questions about sexual health or STIs.

3. The sexual history and physical examination of adolescents (the age of medical consent being 16 years of age, or for mature children generally from the age of 12 years) **should be carried out without the presence of their parents or guardians in order to promote their privacy.** Moreover, sexuality should be included in every adolescent's health interview. Suspicions of STIs in prepubertal children should be directed at ruling out sexual violence.

4. STI screening is appropriate for both individuals who request it and for individuals who have sexual practices identified with risk situations for STIs. The greater or lesser risk of acquiring an STI determines the frequency of screening.

5. The risk of acquiring an STI affects any sexually active person, but there is an increased risk associated with some behavioural practices related to sexual life: the number of sexual partners, the type of sexual partner (stable or casual, recent new partner, partner with STIs, anonymous partners, etc.), inconsistent use of protective measures, sexualised drug use, recent history of another STI, or transactional sex, among others.

6. STI screening in the asymptomatic population should always include serology for HIV, syphilis and hepatitis depending on history (HAV and HBV/HDV) and risk criteria (HCV), as well as molecular techniques for the detection of gonococcus and chlamydia in the sites determined by sexual practices (pharynx, vagina, rectum and urine).

7. To facilitate STI screening in the asymptomatic adult population, self-testing should be promoted in healthcare settings for pharyngeal, vaginal, first urine fraction (males) and rectal specimens (according to evidence of risk).

8. From a cost-effectiveness perspective, for the microbiological analysis of genital and extragenital samples for asymptomatic STI screening, **laboratories should explore the possibility of pooling samples from different sites from the same patient.**

2.1 Sexual history and STI risk assessment

2.1.1 Sexual history in the adult population

In order to address STIs correctly, it is necessary for health professionals to routinely include, as part of the medical history, an assessment of sexual habits and behaviours that may expose individuals to the acquisition or transmission of STIs, including HIV. Clear, respectful and non-judgemental questions, including information on sexual practices, as well as a social and environmental assessment, are crucial for this purpose. All of this is aimed at obtaining a complete sexual history (not forgetting the gynaecological history in women). It is important to determine, in the sexual history, their gender identity, what genitalia/anatomy the individual has and what sexual practices they engage in.

There are five specific aspects of the STI anamnesis that should be considered, which are summarised below. These are merely guidelines and should always be adapted to the circumstances of the individual and the environment. Always remember to start the interview by asking what the reason for the consultation is.

1. Detailed current history.

Signs and symptoms that can guide the subsequent diagnostic and therapeutic approach:

a. Anogenital signs and symptoms:
   I. Presence/absence of anogenital discharge or exudate (including urethral, vaginal, or rectal); dysuria; pruritus; spontaneous pain or dyspareunia; metrorrhagia or postcoital bleeding; pelvic or abdominal pain; testicular pain or swelling; or anal or perianal clinical manifestations.
   II. Presence/absence of anogenital lesions of any kind, especially erosive or ulcerative lesions, present at the time of consultation or in the previous days;
   III. Presence/absence of lymphadenopathies, mainly in the inguinal or cervical areas and determine, if present, whether they are painful or painless.

b. Dermatological signs and symptoms: localised rash or exanthem, or localised lesions of any type, especially of recent onset, and their characteristics.

c. Assess lesions in the oral cavity and/or pharynx.

d. Other signs and symptoms in less frequent sites: conjunctivitis, mono- or pauciarticular arthritis, recent loss of vision or hearing, presence of tinnitus or any neurological symptoms.

e. Systemic symptoms: fever, weight loss, etc.

To complete the anamnesis, remember to ask and note:

- The date of onset, evolution and duration of the aforementioned symptomatology.
- Whether they have received any treatment and clinical response.
- Signs and symptoms reported by sexual partners.

2. Previous history of STIs.

Oriented approach by means of the following guiding questions:

a. *Have you ever been tested for HIV and other STIs?*
Have you ever been diagnosed with an STI? Have you received empirical or targeted treatment for an STI? If so, specify the treatment, duration and response.

b. *Have any of your sexual partners had an STI?*

c. *Have you ever suspected that you might have been infected with an STI, but didn't get tested?*

3. History of sexual practices and behaviours.

For guidance, questions can be based on the following considerations and the interview can be introduced as follows: "To assess the risk of acquiring an STI, I need to ask more specific questions about the type of sexual activity you have had recently":

a. *Are you sexually active?* If so, *what kind of sexual intercourse do you have?*
   I. *Vaginal penetration?*
   II. *Orogenital relations (oral sex)?*
   III. *Anal penetration?* If so*, insertive or receptive?*
   IV. *Have you ever had sex with multiple partners at the same time?*

b. *Do you have regular sexual partner(s)?* If so, *is your relationship open? Is it exclusive?*

c. *When did you last have sexual intercourse?*

d. *How many sexual partners do you usually have in a month, for example? And in the last month? And in the last 3 months?*

e. *What is the biological sex assigned at birth (BSAB) of your sexual partners?*

f. *Have you ever had sex with a person diagnosed with an STI or with symptoms of an STI?*

g. *Have you ever had sex under the influence of alcohol or other recreational substances? If you use them, what substances are they? Is the use oral, inhaled, smoked, injected or other such as rectal?*

h. *Have you been paid or do you pay for sex?* If so, *when was the last time?*

4. STI prevention.

a. Frequency of condom use. For example: *Out of 10 sexual encounters, how often would you use a condom?* If so, *from the beginning or only for ejaculation?* In what type of practices: vaginal, anal or oral penetration?

b. *Have you taken or do you take HIV pre-exposure prophylaxis (PrEP) or any other type of STI prophylaxis?*

c. *Are you regularly screened for STIs?* If so:
   i. *When was your last screening?*
   ii. *What tests were you asked to perform?*
   iii. *Do you know the results of these tests?*

d. *Are you vaccinated against HPV, Mpox, HBV or HAV?*

5. Additional questions.

Is there anything related to your sexual health that you would like to discuss or have questions about? In addition to the above and depending on the specific context, we can introduce more specific questions about the relations such as the use of sexual objects or toys or questions about certain practices.

Despite these suggestions, the accuracy of anamnesis in determining the risk of STIs may be limited due to the possibility that the individual may avoid providing sensitive information during the interview. It is therefore extremely important to interview the patient alone, explaining that questions about their sexual life are necessary for a proper assessment, while always guaranteeing confidentiality (see section 2.1.3 for more detailed guidance on questions that allow inferences of STI risk). Our attitude should be empathetic and non-judgemental, asking open questions, using clear and understandable language for all patients and leaving room for dialogue.

Following the medical history, it is essential to carry out a complete physical examination with special attention to signs that may indicate the presence of an STI.

2.1.2 Sexual history in children and adolescents

a. In the case of pre-pubertal children, the STI anamnesis requires a detailed examination, which must first and foremost be thoroughly oriented towards ruling out sexual violence (see chapter 7 and 8).

b. In the case of adolescents, the irregular use of barrier methods in sexual intercourse at younger ages must be taken into consideration. In addition, the impact of change in social relationships and the difficulty in accessing the health care system guaranteeing their privacy, are causes of the high prevalence of many STIs in this age group. The anamnesis should make it possible to estimate the risk of non-consensual sexual intercourse or the possibility of pregnancy.

It is therefore necessary to include sexuality in every adolescent's health interview, with open, non-judgemental questions, to assess the risk of STI acquisition and to promote comprehensive sexual health and appropriate decision-making. It is essential to carry out the main part of the sexual history and physical examination without the presence of parents/guardians in order to promote intimacy, always in a trusting and non-judgemental environment.

When dealing with adolescents, it is crucial to bear in mind that, in Spain, the age of medical consent is considered to be 16 years of age. The Spanish legal system acknowledges the full entitlement of minors, according to their maturity, from the age of 12. Between 12 and 15 years of age, the child shall be assessed under the concept of “mature child”; that is, a minor with sufficient capacity to make decisions in relation to a specific action, the physician being responsible for assessing the maturity for a specific situation. This responsibility requires a shared reflection with the minor, ensuring confidentiality, and agreeing with them what can be shared with the parents/legal guardians. We always seek the greatest benefit for the minor, taking into account that our patient is an adolescent.

2.1.3 STI risk assessment

In the context of obtaining a medical history, it is necessary to make an individualised assessment of each person's risk of acquiring an STI in order to reduce the "*missed opportunities*" in the detection of new infections. This will not only allow us to better decide on the diagnostic tests to be performed, as well as on the types of samples to be collected, but should also be an opportunity to raise awareness in order to strengthen primary prevention, health education, information, counselling, and offer vaccinations.

The questions proposed in the anamnesis phase should be aimed at inferring the risk of acquiring an STI. It is easy to assume that any affirmative answer to the 10 key questions described below (which do not exclude the extensive questionnaire described in the previous phase) already indicates a

risk of acquiring HIV and other STIs, which increases proportionally as the number of affirmative answers increases:

1. Multiple sexual partners or sexual partner with multiple concurrent partners
2. Sexual practices with a person diagnosed with or recently treated for an STI
3. New sexual partner in the last 12 months
4. History of STIs
5. Sexual practices with sex workers
6. Use of alcohol or other substances associated with sexual practices (e.g. chemsex)
7. Inconsistent condom use with sexual partners
8. Use of social media and apps to search for sexual encounters
9. Group sex, swinging, orgies, sessions, chills, etc..
10. In addition, we must take into account especially vulnerable populations for the acquisition of STIs:
    - Adolescents and young people: They are a particularly vulnerable group, as they are more likely to engage in high-risk sexual behaviour. However, it is estimated that about 10% are regularly screened for STIs. The under-25 age group is included in the main STI guidelines as a group of special epidemiological interest.
    - Gays, bisexuals and other men who have sex with men (GBMSM)
    - Victims of sexual violence
    - Transgender people
    - Persons deprived of liberty

2.2 STI screening in different populations

2.2.1 STI screening in the general population.

The implementation of proactive STI screening strategies is of particular importance, as STIs are most often asymptomatic or subclinical for long periods of time. By diagnosing the presence of an STI in an asymptomatic person, we can not only treat the infection and prevent further sexual and reproductive health complications, but also minimise transmission during sexual contact.

It is recommended that STI screening be offered, and performed when appropriate, when any of the following conditions are met:

- A person who voluntarily requests STI screening.
- A sexually active person in an exclusive relationship, at the beginning of each new relationship, after after a change of sexual partner.
- A sexually active person with multiple partners (in open or exclusive relationships) after the last screening.
- Pregnant women according to reference guidelines (see section on special populations).

- A person who, during the anamnesis, is considered to be at increased risk of acquiring an STI (see sections on anamnesis andriskassessment).

For those people who meet one or more of the above situations, comprehensive STI screening should be regarded by health professionals as good clinical practice.

2.2.2 Periodicity of screening.

The recommended frequency of STI screening in asymptomatic individuals will depend on their increased or decreased likelihood of exposure to STIs. In line with other international guidelines, such as BASHH, at least three groups could benefit from this screening based on the likelihood of exposure to STI acquisition:

a. Anyone in a mutually monogamous relationship: testing is recommended at the beginning of the relationship.
b. Sexually active people: screening is recommended annually and after a change of partner up to a maximum of once every 3 months.
c. Sexually active people at high risk of STIs (PrEP users, more than 10 sexual partners in the last 12 months, multiple or anonymous sexual partners since last STI, sexualized drug use (chemsex) or first year after an STI): could be recommended every 3 months.

It is important to note that living with HIV, belonging to the GBMSM subgroup, being a transgender person or belonging to other diverse populations cannot be used in isolation as a criterion for STI risk, unless other associated factors co-exist.

2.2.3 How to screen for bacterial STIs and which sites should be screened

STI screening in an asymptomatic population should be approached comprehensively. Although many diagnostic platforms offer multiplex panels for the simultaneous detection of multiple pathogens, the clinical relevance of some of these findings remains uncertain and should be interpreted conservatively..

The current consensus for screening in asymptomatic populations includes serological testing for HIV, syphilis and viral hepatitis (HBV, HCV), as well as nucleic acid amplification techniques (NAAT) for the diagnosis of *N. gonorrhoeae* and *C. trachomatis*. Serological screening for HAV vaccine markers will be included in epidemiological settings where faecal-oral transmission of HAV is possible. Conversely, while information may be available in panel systems for multiple pathogens, most international guidelines do not recommend routine screening for *Trichomonas vaginalis* (TV), *Mycoplasma genitalium* (MG), *Gardnerella vaginalis* (GV) in asymptomatic populations or human papillomavirus (HPV) infection in the general population (for which specific screening programmes exist).

The following table shows which pathogens and which microbiological tests are to be considered in STI screening of asymptomatic persons:

Blood (serum) tests

Pathogen	Recommended population	Recommended test	Remarks
HIV.	All.	ELISA 4G. Requires confirmatory test, either by WB1 or NAAT if primary infection is suspected.	Repeat if there is a risk of recent exposure (currently, the detection rate of ELISA 4G is 95% with a 2-4 week window; with a 6 week window, the rate is almost 100%). Consider NAAT in patients starting PrEP.
***T. pallidum*.**	All.	Treponemal serology if there is no previous history (followed by non-treponemal testing, if reactive) and non-treponemal serology (RPR or VDRL) in patients with previous treated syphilis.	
HBV (if there is no known previous history of infection or immunity or complete vaccination schedule).	GBMSM, transgender people, multiple partnerships, sex workers, PHIV, PWID, sexual assault, HBV partners, people from endemic areas.	HBcAb serology (IgG+IgM) +/- HBsAb. In case of HBcAb positive, include HBsAg.	Vaccinate individuals without documented seroconversion.
HCV.	Not recommended in the general population, only for populations with some risk criteria (GBMSM, transgender people, people living with HIV (PLHIV), injecting drug users (IDUs)...).	Primary screening antibody serology (HCVAb). If HCVAb positive, perform any strategy that allows single-step detection of the viraemic patient (HCV-RNA or HCV-Ag).	
HAV (if there is no known previous history of infection or immunity or complete vaccination schedule).	GBMSM, transgender people who have sex with men, PWID, people with HBV/HCV.		

Molecular tests (NAAT) on genital and extragenital samples

Blood (serum) tests			
Pathogen	Recommended population	Recommended test	Remarks
NG/CT.[2]	*Cis* men / people with a penis. *Cis* women / people with a vagina. GBMSM.	First-void urine (FVU) or at least no urination in the previous 2-4h. Vaginal swab (promote self-collection if authorised).[3] Pharyngeal and/or rectal swab[4] (promote self-collection if authorised).	In *cis* women, the vaginal swab is more sensitive than the urine sample. In the case of colposcopy, an endocervical sample may be collected instead of a vaginal sample. For GBMSM, it is recommended to take samples at 3 anatomical sites (urine, pharynx, rectum).[4] Some suggest analysis by pooling samples from the same patient ("*pools*").[5]
MG.	Screening is NOT recommended.	First-void urine (FVU) or at least no urination in the previous 2-4h. Vaginal swab (promote self-collection if authorised).	Consider only in case of regular partner contact with therapeutic intent.
***T. pallidum*.**			NAAT tests should not be performed in the asymptomatic population.
Remarks			
Extragenital samples			
Pathogen	Recommended population	Recommended test	Remarks
NG/CT2.	Screening is not recommended for cis women, except for women with receptive anal practices, and/or oral sex and/or high risk of acquisition by a partner diagnosed with an STI.	Pharyngeal and/or rectal swab.	For GBMSM, it is recommended to take samples at 3 anatomical sites (urine, pharynx, rectum).[4] Some groups suggest analysis by pooling samples ("*pools*").[5]

Table 1. Recommendations for STI screening of blood- and body fluid-borne pathogens in asymptomatic populations, according to BASHH guidelines. [1] WB Western-Blot. [2] All CT of rectal or pharyngeal origin in the GBMSM population should be genotyped to identify the presence of genotypes associated with lymphogranuloma venereum. [3] In cis women, the vaginal swab is more sensitive than urine. On the other hand, if a speculum exam is performed, endocervical sampling is indicated instead of vaginal sampling. [4] In GBMSM and transgender people without receptive anal practices, rectal infection can occur if genital infection is present. [5] If a pooling strategy is chosen, all positive CT shall be genotyped for LGV.

In authorised situations, self-collection of vaginal, rectal and pharyngeal samples is considered a valid alternative to collection by healthcare personnel, especially in asymptomatic individuals and in a healthcare setting.

Based on the risk assessment (which allows inferring which individuals may benefit from screening) and the recommendations described in the table above, a detailed description of the types of samples and how to perform sampling in the asymptomatic population is presented.

- **Genital samples:**
  - First-void urine (FVU), first 15-20 mL (preferred to urethral swab) or at least 2-4 hours without urination, for asymptomatic urethral infection in people with penis, irrespective of the use of barrier methods.
  - Vaginal swab, irrespective of the use of barrier methods, by self-collection. If colposcopy is performed, an endocervical sample collected by a healthcare professional can be used.

- **Extragenital samples:**
  - Self-collected rectal swab for rectal infection, indicated for GBMSM, transgender people and other people with receptive anal practices.
  - Pharyngeal swab collected by a healthcare professional or self-collection if instructions are possible, for suspicion of infection in this site. Pharyngeal screening for CT may be considered in individuals with relevant oral sexual exposure although the clinical and epidemiological impact of routine screening remains uncertain. Any positive result of NG in the pharynx obtained by NAAT should be confirmed by a second technique.
  - Extragenital screening is not recommended for cis women except for risk indicators such as a diagnosis of NG or CT in a sexual partner or sex workers.

The analysis of genital/extragenital samples for the diagnosis of asymptomatic STIs can be performed individually or by pooling samples ("*pools*") using different strategies.

For asymptomatic screening in groups with a high incidence of STIs (GBMSM, transgender people, sex workers...), genital and extragenital samples from the same individual can be pooled in a single NAAT assay. If so, all CT must be genotyped to rule out the presence of LGV and patients with positive NG should be treated with ceftriaxone 1g due to the risk of pharyngeal gonorrhoea.

It is assumed that not knowing the anatomical site of infection may be irrelevant for providing empirical treatment or establishing contact screening strategies.

- In screening groups with low STI incidence, while there is experience with this strategy, there are still concerns about the loss of sensitivity, and the number of samples per pool. Therefore, a higher level of evidence and more defined procedures are required to support this proposal.

2.2.4 Where to screen

Every contact with the healthcare system represents an opportunity to assess risk and offer screening, where appropriate. .

Proper coordination between different levels of care and diagnostic laboratories will reduce the number of missed opportunities for STI screening. While there are circumstances or populations which are difficult to access (sex workers, transgender people or migrant populations) where efforts should be made to ensure that asymptomatic screening is offered in places frequented by these people, it is necessary to promote decentralised diagnostic approaches, such as the implementation of point-of-care (POC) or dried blood spot (DBS) strategies, but always under the supervision and logistical control of health professionals.

SCOPE	STRENGHTS	WEAKNESSES
Primary Care	- It is the gateway to the health system, making it an ideal environment for screening. - The approach to patient care is comprehensive and cross-cutting, which supports the provision of STI screening regardless of the reason for consultation based on behaviours that increase the likelihood of acquiring STIs. - Primary Care teams know the patient's environment and living conditions, and carry out community actions and health education, which are crucial activities to control the transmission of STIs.	- Not all Primary Care centres have ceftriaxone available for IM administration to patients diagnosed with gonococcal infection, so some physicians refer patients to hospital centres for investigation and treatment. - Some patients may be more reluctant to discuss STIs with the same professional who cares for their family. - Sample collection for STI screening and diagnosis is not always available in Primary Care centres, especially during emergency hours. - There is a lack of specific training in the management of STIs. This, combined with overloaded care, can make it difficult to provide care.
Hospital care and STI clinics	- Availability of sample collection and administration of specific treatments during the consultation, which optimises the actions carried out in a single act. - STI specialists, who practically ensure that up-to-date protocols and guidelines are followed.	- More limited accessibility to Hospital Care consultations, especially for populations with legal, bureaucratic or linguistic barriers. - Not all specialities have the same perception of STI risk among their patients, increasing missed opportunities.

Table 2. Main strengths and weaknesses of different care settings in STI screening, based on the authors' experience.

2.2.5 Specific populations

Depending on the social determining factors of health, there are certain groups of special epidemiological interest where STI transmission among these populations may be more concentrated. The identification of these key populations allows for more efficient screening strategies:

2.2.5.1 Migrants and refugees

Migrant populations may face a number of barriers in accessing the health system (administrative, economic, linguistic, cultural, etc.). Various studies and experiences suggest that health education programmes and linguistically and culturally adapted health care for these groups improve their relationship with our health system, their knowledge, attitudes and practices, facilitating adherence to medical follow-up and treatment. If there is a language barrier or cultural differences between the healthcare professional and the patient, it is recommended to work with intercultural mediators to improve communication.

HIV and syphilis screening is recommended for migrants and refugees from areas of high HIV prevalence (>1%). For other STIs, risk factors will be taken into account, both in the countries of origin and destination and during the migration journey. The sexual history should be aimed at identifying these risk factors, such as a history of sexual violence, multiple sexual partners or previous history of STIs, as well as possible pregnancy or signs and symptoms of STIs at the time of assessment. Because of the significant risk of sexual assault during the migratory journey, it is important to include questions about it in the anamnesis.

2.2.5.2 Pregnant women

In cis women and other pregnant people, a sexual history should also be carried out and emphasis should be placed on STI prevention during this period of special relevance due to the possible vertical transmission during pregnancy or breastfeeding. Screening for STIs is recommended at the frequency recommended in the general population depending on the situation and risk practices. Therefore, screening should be done at least in the first trimester and, if negative, consider repeating it in the second and third trimester and during labour. Screening for HIV and other STIs should be carried out at the time of labour in all pregnant women/people who have not attended prenatal check-ups.

Screening for CT and NG is recommended for all pregnant women under 25 years of age and for women over 25 years of age who are at increased risk of acquiring CT and NG. The test should be performed at the first prenatal visit. Pregnant people who remain at risk should also be screened again in the third trimester to prevent postnatal complications and infection in the newborn.[50]

2.2.5.3 Children and adolescents

As mentioned in section 2.1.2 (anamnesis in children and adolescents), STI screening, in the case of pre-pubertal children, mainly takes place in the context of suspected sexual violence (see corresponding chapter). On the other hand, it may be necessary to screen for vertical transmission, especially if the child comes from places where full prenatal screening has not been performed (e.g. HIV, HBV, HCV, syphilis) or in cases of accidental, self- or hetero-inoculation transmission. On the contrary, for adolescents, screening should be considered in the context of an active sexual life, following at least the screening frequency recommended in the general population according to the risk factors described above.

Adolescents have some particularities that need to be taken into account for STI screening:

a. Recommendations for adolescent screening:
   I. Routine annual screening for CT and NG is recommended for sexually active adolescent females and, based on sexual practices and other risk behaviours, in sexually active males.
   II. Offer syphilis and HIV testing to sexually active adolescents at age 15 and at varying intervals depending on sexual practices.
   III. In asymptomatic adolescents, screening for other STIs (trichomoniasis, HPV, HAV and HBV) should be individualised.

b. Recommendations for improving adherence to screening in adolescents:
   I. Screening by self-collection in adolescents with vagina and first urine stream in adolescents with penis should be considered to increase the acceptability of screening. (see reference 12)
   II. The results of the tests requested should be collected, as the adolescent, especially when asymptomatic, may not be regular in follow-up consultations, often hampered by difficulties in accessing the health system.
   III. Adherence to adolescent STI screening guidelines should be monitored.

2.2.5.4 Men who have sex with men

The risk of acquiring viral or bacterial infections through sexual contact will depend on the number of sexual partners, the gender of the partners and the sexual practices reported. As mentioned above (section 2.2.2), regular screening is of particular relevance when there is sexualised drug use or sex clubs/cruising areas. Where STIs are diagnosed, screening should be included at all sites according to sexual practices, including serology for HIV, syphilis and hepatotropic viruses.

2.2.5.5 Women who have sex with men and women (WSMW) and women who have sex with women (WSW)

WSMW have a similar or somewhat lower risk of acquiring viral or bacterial infections through sexual contact than women who have sex only with men. WSW appear to have a lower incidence of STIs than women who have sex with men and women. However, they are not negligible. In addition, it should be noted that they may have had male sexual partners in the past. Numerous studies show that the use of barrier methods (such as condoms for sex toys, or gloves for digital-genital sex) is unusual among women who have sex with women. Therefore, health professionals should not assume a low risk for STIs in this group. Trichomoniasis is more prevalent in this group than CT or NG infections, and direct transmission between female sexual partners has been demonstrated. HSV and HPV can be transmitted between women; therefore, they are also at risk of developing cervical cancer, even if they have not had male sexual partners. Epidemiological data clearly demonstrate that bacterial vaginosis is sexually transmitted among women with female sexual partners. However, as in other groups, the risk will depend on the number of sexual partners, the gender of the partners (higher risk when sexual partners include men), the sexual practices used and the preventive methods used. The risk of acquiring an STI if their partners are GBMSM is very high and in this case they could benefit from the same screening (and preventive interventions) as GBMSM. Considering the factors referred to in the anamnesis, STI and HPV screening is indicated for all WSMW or WSW according to current recommendations.

2.2.5.6 Transgender people and other diverse populations.

The risk of transgender people acquiring viral or bacterial infections through sexual contact will depend on the number of sexual partners, the gender of the sexual partners (higher risk when sexual partners include men) and the preventive practices and methods used.

Key aspects to identify and gather in the initial clinical history for this population group would be:

- Genitality / gender reassignment surgery: it may condition sexual practices and determines sample collection for bacterial STIs.
- Sex workers.

2.2.5.7 Sex workers.

The risk of acquiring an STI in this group is considered high overall given the frequent association with other risk indicators: high number of sexual partners, suboptimal use of barrier methods or substance use during sex. Individualisation is advised by prioritising frequent screening at genital and extragenital sites. Periodic screening should be maintained for as long as transactional sex practices continue and for up to 3-6 months after cessation of transactional sex.

2.2.5.8 Population deprived of liberty

Sexually active people in correctional or penal institutions are at risk of acquiring viral or bacterial infections through sexual contact, depending on the number of sexual partners, the gender of the sexual partners (higher risk when sexual partners include men), and the sexual practices and preventive methods used. A history of injecting drug use, which is more prevalent in this population, is also a factor associated with a higher risk of HIV and HCV than in the general population. Screening for HIV, HBV and HCV on admission is recommended. Screening for other STIs (NG, CT) and cervical cancer follows the same guidelines as in the general population. Screening for TV may be recommended in high-prevalence geographic areas and/or in women with associated risk factors (**IIB**). Screening for syphilis could be recommended based on the prevalence of early forms, both institutionally and geographically.

2.3 Health education and contact tracing

2.3.1 Health education

Sexual health is understood as the greatest possible degree of enjoyment of a healthy, pleasurable and egalitarian sexuality that promotes joint responsibility and equality in affective and sexual relationships and emotional well-being. Sexual health requires a positive and respectful approach to sexuality and sexual relationships, as well as the possibility of having pleasurable and safe sexual experiences, free from coercion, discrimination and violence. [14] In this sense, education in this matter is an essential foundation as it empowers people to enjoy their sexuality in a healthy and safe way. [15] Its approach must be holistic and include key concepts such as relationships, affectivity, sexuality, gender, violence, consent, autonomy, body image, reproductive health and STIs, from an approach based on human rights, respect and non-discrimination, gender and sexual diversity, and the social determinants of health. From a healthcare perspective and focusing on STI prevention, including HIV, both interactive and high-intensity behavioural counselling and motivational interviewing are effective strategies for STI prevention. However, despite its growing and considerable magnitude, studies evaluating health education strategies for STI prevention are very limited.

A major study by the *United States Preventive Services Task Force* concluded with moderate certainty that assisted sexual behaviour counselling interventions reduced the likelihood of acquiring an STI in sexually active adolescents and adults at increased risk, such as those with a current STI, those who did not use condoms or those with multiple sexual partners, with a significantly high net benefit. The general recommendation should be to be able to offer assisted sexual health counselling to all sexually active adolescents and to any adult at increased risk of STIs (evidence B).[16]

Information on safer sex should be part of all sexual health consultations and should include:

1. Promotion of sexual diversity and prevention of situations of violence.
2. Consent to sexual relations.
3. Transmission mechanism of STIs.
4. Types of sexual practices and risk reduction.
5. Barrier methods and their effectiveness, limitations and correct use.
6. Drug use and risk reduction.
7. Vaccines and other prevention methods.

Patients with an STI should be informed about the causative agent of the STI and its transmission, the treatment to be taken (dosage, duration, possible side effects, importance of compliance etc.), the need to abstain from sexual intercourse until one week after completion of treatment and, if necessary, until the contacts have been traced and treated. It may be helpful to provide the patient with written information about the infection they have had. There are Spanish associations and NGOs with very well elaborated information material that should be incorporated into the STI/HIV consul-

tations as support material for the explanations we offer to our users. (E.g.: STOP, Adhara, gtt-VIH, gays positius, etc). It is available in several languages, which would make it easier for foreign users to understand.

2.3.2 Contact tracing

Contact tracing is a confidential process by which sexual contacts are informed that they have had contact with an STI and are offered care and treatment by a health professional (see Table 3).
This contact tracing has clinical and public health benefits:

1. It prevents re-infection of the index case.
2. It diagnoses and treats people who may be infected and who may also be asymptomatic.
3. It breaks the chain of transmission of infection at the public health level.

Table 3. – Time periods, depending on the syndrome or Microorganism, for intervention on sexual contacts.

Syndrome	**Recommended time periods for notification**
Non-specific urethritis/ cervicitis	Symptomatic persons: from the previous 4 weeks.
Pelvic inflammatory disease.	Sexual partners in the last 6 months should be screened.
Scabies	From 2 months prior to symptom onset.
Pediculosis	From 3 months prior to symptom onset.
Sexually transmitted enteric infections (STEI)	Recommendations: - Trace all contacts from the 4 weeks prior to symptom onset (except for *E. histolytica proctitis*) - Symptomatic and asymptomatic contacts of *E. histolytica* should be tested and those positive should be treated. - Symptomatic contacts of other enteric infections should be treated considering the same pathogen as the index case.
Aetiology	**Recommended time periods for notification**
Chlamydia trachomatis	Symptomatic urethritis/cervicitis: From 2 months prior to symptom onset.
	Rest of index cases (asymptomatic or with symptoms in a different location): 6 months.
Neisseria gonorrhoeae	Sexual partners in the 2 weeks prior to symptom onset or any sexual partner with symptoms, regardless of time, in gonococcal urethritis. All sexual partners in the 60 days prior to symptom onset if the infection is from sites other than the symptomatic urethral site.
Mycoplasma genitalium	Only current and recurrent sexual partners should be screened and treated
Lymphogranuloma venereum	Sexual contacts of symptomatic index case: From 2 months prior to symptom onset.
	Sexual contacts of asymptomatic index case: From 2 months prior to diagnosis.
Treponema pallidum	
Primary syphilis	From 3 months prior to symptom onset.

Syndrome	Recommended time periods for notification
Secondary syphilis	From 6 months prior to diagnosis.
Early latent syphilis	From 12 months prior to diagnosis.
Late latent or indeterminate syphilis	Up to the date of the most recent negative serology if available; otherwise, backtrack the sexually active life of the index case as far as possible.
HSV-1 / HSV-2	Although there is no specific time period, it may be helpful in detecting possible cases in contacts who are unaware of the symptoms.
Molluscum contagiosum	No sexual contact tracing is required.
Trichomonas vaginalis	From 1 month prior to symptom onset.
HAV	Notify contacts from two weeks before and one week after the onset of jaundice.
HBV	Contact tracing should include any sexual contact (vaginal or anal sex or oro-anal sex) or needle-sharing partners from two weeks before the onset of jaundice until a negative surface antigen (negative HBsAg) is achieved. In cases of chronic infection, trace contacts until any episode of jaundice or until such time as the infection is considered to have been acquired, although this may be impractical for periods longer than 3 years.
HCV	If it is acute hepatitis C: Contact tracing should be conducted if the index case or partner is HIV+ (vaginal, anal or oro-anal sex) or for needle-sharing partners during the period in which the index case is considered to have been infectious. If it is chronic hepatitis C: If there is no acute infection, contacts should be traced up to the most likely date of infection (e.g. transfusion, needle exchange, etc.), although this may be impractical for periods longer than 2-3 years.
HPV	There is no specific period or recommendations.
HIV	If the probable date of infection can be estimated, screen all contacts from the date of infection and within the previous 3 months. If this is not possible, backtrack to the date of the most recent negative serology if available; otherwise, backtrack the sexually active life of the index case as far as possible.
Mpox	Close contacts from 21 days after diagnosis. (Ministry of Health 2022 protocol).

Adapted from the British Association of Sexual Health and HIV Sexually Transmitted Infections guidelines.[17]

There are four basic modes of contact notification:

- Patient referral: the referral is made by the index case;
- Provider referral: the referral is made by a healthcare professional;
- Conditional referral: the index case assumes responsibility for the referral, but if after a period of time it has not been made, it is passed on to the healthcare professional;
- Dual referral: the referral is made anonymously by the patient and/or the healthcare professional using applications and digital tools which, via text message, are responsible for notifying sexual contacts.

Patient referral can be reinforced by providing written information about the infection to be given to contacts. In some countries, Expedited partner therapy or Delivered partner therapy is used, where medication is dispensed to the index case to be given to their contacts.

Contact tracing should be done as early as possible in order to minimise re-infection and prevent disease progression in infected partners. In addition to the appropriate tests for the diagnosis of the infection to which they have been exposed, other STIs should be ruled out (**A-III**). The chosen method will depend on the availability of resources and the acceptance by the patient and their contacts. If possible, the conditional referral strategy is recommended; if not, at a minimum, the patient referral strategy is recommended, reinforced by providing the patient with written material (**A-III**).

2.3.3 Vaccination against STIs

Vaccination is one of the most effective methods of preventing infectious diseases. For STIs, vaccines against HAV, HBV, HPV and Mpox virus are currently approved. In patients who are vaccinated against HAV and HBV, serological markers are recommended to confirm the absence of immunity against these viruses before starting the vaccination schedule.[18,19]

2.3.3.1 Hepatitis A

In immunocompetent individuals, the recommended vaccination schedule consists of two doses, with a first dose on day 0 and a booster dose at 6 after 6 months. It is indicated for people with sexual practices that may carry an increased risk of acquiring HIV infection (sex workers, GBMSM, people who have anal-oral sex or inject drugs) and for people with HIV infection or chronic liver disease.[18]

In PLWHIV with less than 200 CD4/mm³ and/or detectable viral load, a worse response to vaccination[20] and a shorter duration of seroprotection[21] have been described. The current recommendation in our setting is to administer 3 doses of vaccine (at 0, 1, 6 months) if the patient's CD4+ T-lymphocyte count is < 350 cells/mm³ at the time of vaccination, or two doses (at 0 and 6 months) if it is higher. Post-vaccination serology is recommended 2-3 months after the last dose, with an additional dose of vaccine administered if serology remains negative. It is also recommended to administer booster doses every 10 years to individuals who remain at risk of exposure.[22]

In HIV-infected children and adolescents, monitoring of post-vaccination seroprotection status is recommended at 4-6 years, 9-11 years and 14-16 years. In case of markers below protective level, re-vaccination should be considered.[23]

2.3.3.2 Hepatitis B

The vaccination schedule includes three doses with a first dose on day 0, a second dose at one month and a third dose at 6 months. In previously unvaccinated children up to 18 years of age, a 3-dose schedule (0-1-6 months) shall be administered.[24] Subsequently, vaccination is recommended for people with risk factors: GBMSH with multiple sexual partners, people who inject drugs, contact with HBsAg carriers, HIV or HCV infection or chronic liver disease, transplant recipients, blood product recipients or healthcare workers at occupational risk. Post-vaccination serological markers may become negative over time. In individuals at high risk of infection, a booster dose would be recommended and subsequently assess serological response by quantification of anti-HBs. If anti-HBs titres are >10 mIU/mL, an adequate response can be confirmed and the individual should be considered adequately immunised, with no further doses required. Conversely, if anti-HBs titres remain <10 mIU/mL, completion of the standard vaccination schedule (0–1–6 months) is recommended, followed by repeat post-vaccination serology one month after the last dose. If anti-HBs titres persist at <10 mIU/mL, the individual should be considered a non-responder to the vaccine and no further vaccination courses are recommended. In non-responders to an initial schedule, a second one is recommended.

In PLHIV, the vaccine response may be lower, so it is recommended to confirm seroconversion by assessing anti-HBs titres between the first and second month after completion of vaccination. In the absence of a serological response, revaccination would be indicated. Strategies to improve the immune response may include administration of a standard vaccination schedule (0–1–6 months) at double dose, a four-dose schedule (0–1–2–6 months), or deferring vaccination until a CD4 cell count >200 cells/mm³ has been achieved.[21]

2.3.3.3 Human Papillomavirus (HPV)

- Systematic vaccination of girls and boys at age 12, .1-dose schedule.
- Recruitment of unvaccinated males and females up to and including 18 years of age. 1-dose schedule.
- Unvaccinated individuals with certain risk situations up to and including 45 years of age.
- 1 dose up to the age of 25 years and 2 doses from the age of 26 years, at least 6 months apart:
  - Men who have sex with men.
  - People engaged in sex work.
- In unvaccinated immunosuppressed individuals belonging to the following risk groups, and up to and including 45 years of age, a 3-dose schedule (0, 1-2 and 6 months) is always recommended, regardless of the age of commencement of vaccination, including:
  - WHIM syndrome (IDP): vaccine covering types 6 and 11.
  - HIV infection.
  - Solid organ or haematopoietic stem cell transplantation (irrespective of previous vaccination status in HSCT).
- If one or two doses have been received previously, complete vaccination up to 3 doses.
- Women, regardless of age, who have received any treatment for a high-grade intraepithelial lesion of the cervix (CIN2+). 3-dose schedule (0, 1-2 and 6 months). Vaccination should preferably be carried out before treatment of the lesion or, if this is not possible, as soon as possible after the end of treatment.
- In any of the above recommendations, a 3-dose schedule should be administered in case of immunosuppression. [49]

2.3.3.4 Mpox

Following the first reported cases in May 2022, the Mpox outbreak was declared by WHO as a public health emergency of international concern in July 2022. Vaccination in Spain started in June 2022 and is being conducted with a vaccine under two brand names (IMVANEX and JYNNEOS). These vaccines against classical smallpox have demonstrated cross-immunity against both viruses.[24] The standard smallpox vaccination schedule is 2 doses, the first dose on day 0 and a booster dose at one month. Vaccination is recommended in two situations: pre-exposure prophylaxis and post-exposure prophylaxis, prioritising pre-exposure vaccination in people under 45 years of age with high-risk sexual

practices.[25] Currently, the subcutaneous route (0.5 ml) has been prioritised for the administration of this vaccine. However, the intradermal route (0.1 ml) may be used in case of dose limitation or other special situations that make this route of administration more appropriate.[25]

The recommendation of population groups to be vaccinated will be maintained:

2.3.3.4.1 Pre-exposure prophylaxis

- People who engage in unprotected sexual practices, especially but not exclusively, GBMSM.
- Persons at occupational risk, such as healthcare professionals in STI/HIV clinics caring for people with high-risk practices and laboratory staff handling samples potentially contaminated with Mpox virus or staff involved in surface disinfection in specific premises where unsafe sex takes place, whenever the appropriate use of personal protective equipment cannot be ensured. Currently, pre-exposure vaccination is not recommended for children under 18 years of age.

2.3.3.4.2 Post-exposure prophylaxis

Immunisation is recommended for all close contacts who have not had the disease, including adolescents.[24] Vaccination should take place within 4 days of first contact (although it may be offered up to 14 days if there are no symptoms). The recommended post-exposure vaccination schedule is one single dose. The schedule will be supplemented with another dose in people with risky sexual practices. In people with a history of smallpox vaccination, it may also be considered not to administer the second dose.

2.3.3.5 Other vaccines: 4CMenB

In the UK, the meningococcal vaccine 4CMenB (Bexsero®) has recently been approved not only for GBMSM, but also for all those individuals potentially at risk of acquiring a gonococcal infection (recent history of gonorrhoea or other STI, a new diagnosis of gonorrhoea, or having unprotected sex with multiple partners). The UK's Joint Committee for Vaccination and Immunisation based its decision on the results of studies conducted in New Zealand, Australia and the United States, in which a reduction in the risk of contracting gonorrhoea in vaccinated individuals was found to be between 31% and 42%. [26-28] Moreover, this measure could prove to be cost-effective.[29]

2.3.4 Epidemiological surveillance

2.3.4.1 National epidemiological surveillance system

Population-based epidemiological information on STIs in Spain comes from the National Epidemiological Surveillance Network (RENAVE). [30] In Spain, the STIs currently included among the notifiable diseases are gonococcal infection, syphilis, congenital syphilis, *Chlamydia trachomatis* infection (genotypes D-K) and LGV (*C. trachomatis* genotypes L1-L3). Most of them are now reported on an individual basis, although it is in the process of being implemented in some Autonomous Communities, so the comparison of incidence rates is limited by the differences in the surveillance systems in the Autonomous Communities.[31]

2.3.4.2 Epidemiological data

In 2016-2022, of the STIs considered notifiable diseases, *C. trachomatis* infection had the highest incidence, especially among women aged 20-24 years.[31] *Neisseria gonorrhoeae*, *Treponema pallidum* and LGV infections were more frequent in men aged 25-34 years. All of these STIs increased over the period, with the exception of 2020 due to the COVID-19 pandemic.

IUSTI recommends that *Mycoplasma genitalium* [32]infection be included in the syndromic diagnosis of symptomatic STIs. Although it is an infection that has been described relatively frequently in different local studies, there are no official data published in Europe or Spain on its incidence rates.

2.3.4.3 Antibiotic resistance surveillance

At the national level, there is currently no reporting and surveillance system for antibiotic resistance in the microorganisms that cause the main treatable STIs: *N. gonorrhoeae, M. genitalium, C. trachomatis* and *T. pallidum*. However, in recent years, several studies have been published in Spain, the results of which coincide with those described in other European countries.[33-35]

The situation with *N. gonorrhoeae* and *M. genitalium* is of interest. In the case of gonococcus, resistance to ceftriaxone, the antibiotic of choice, remains below 0.3% in Spain and is currently negligible in Europe as a whole (https://www.ecdc.europa.eu/en/publications-data/gonococcal-antimicrobial-susceptibility-surveillance-eu-eea).[33] In contrast, the rate of macrolide resistance has steadily increased from 3.6% in 2016 to 25.6% in 2022, calling into question their empirical use in dual therapy. In the case of *M. genitalium*, the rate of macrolide resistance has increased. Therefore, its susceptibility needs to be analysed using NAAT that detect mutations in the 23S rRNA gene associated with its resistance in order to implement a targeted treatment. Quinolone resistance rates have also increased, mainly associated with the S83I mutation of the *parC* gene.[36-37]

Despite occasional treatment failures in *C. trachomatis* infections, no resistance to macrolides, the most commonly used antibiotic in the treatment of *C. trachomatis*, has been detected in Spain.[34] Fi-

nally, as an alternative to penicillin as the treatment of choice for *T. pallidum* infection, tetracyclines have resistance rates of 0% compared to 95% for macrolides.[35]

2.3.4.4 Value of molecular epidemiology

Molecular characterisation studies carried out in Spain in recent years have allowed us to gain a deeper understanding of the transmission characteristics of *C. trachomatis, N. gonorrhoeae, M. genitalium* and *T. pallidum* infections in our environment.[35, 37-41]

In the case of infection with *C. trachomatis*, different transmission dynamics have been observed depending on sexual behaviour: in GBMSM, the most frequent genotypes were D, G, J, L2; in women and men who have sex with women, genotypes E and F were more frequent, with a different and more diverse distribution of sequences. In small outbreaks of *N. gonorrhoeae* infection with high resistance to azithromycin, isolates belonging to MLST ST7823/NG-MAST ST5309 in MSW and to MLST ST9363/NG-MAST ST3935 in GBMSM have been identified.[41] In the case of *M. genitalium*, genetic characterisation has made it possible to distinguish between persistent and recurrent infections in cases of treatment failure despite adequate targeted treatment in which macrolide resistance-associated mutations developed mainly during treatment (making contact tracing and test of cure essential to the management of this infection), and to rule out clonal dissemination as a possible cause of increased macrolide resistance.[42, 43] Finally, in the case of *T. pallidum*, the most frequently detected genetic profiles were 1.3.1 (56%) and 1.1.1 (11%).[31]

2.3.5 Addressing STIs in the third sector: role, screening and diagnosis, referral and access to care

2.3.5.1 The role of community-based NGOs

The United Nations' 2021 Political Declaration on HIV and AIDS, in line with the Paris Declaration (2014) on fast-track to ending the HIV epidemic, and the Seville Declaration on the centrality of affected communities (2022) makes it clear that we will not achieve our goals of ending the HIV epidemic by 2030 (the UNAIDS declaration refers to eliminating HIV as a public health problem rather than ending the epidemic), without the meaningful involvement of key communities, and calls for an explicit commitment to ensure that they are included in all aspects of the responses. This commitment should be similarly integrated into local responses to tuberculosis, viral hepatitis and other infections. (UNAIDS, 2022).

Community-led services have a greater impact, in terms of improved access and increased coverage, compared to other types of service provision. They lead to better health outcomes and can facilitate a scale-up and acceleration of interventions through demand creation, especially in communities with the highest barriers to accessing the health system.[44] Community-based NGOs generate this demand and provide services directly, be it health interventions, psychosocial care or interventions related to legal and human rights. They humanise and improve the quality of care, provide expertise and combine the lived experience of individuals and key populations. Given the high levels of stigma experienced by people living with HIV and other key populations in screening for other STIs and in accessing the health system, training of health professionals is a critical component within these resources[45], including awareness-raising activities on sexuality and communication that contribute to destigmatization.

The benefits of offering rapid testing in community settings are recognised in these global strategies, which propose that by 2026, up to 30% of diagnostic testing and treatment services should involve the community, as well as in one of the cross-cutting approaches (4.3. Community engagement approach and actions based on scientific evidence and innovation) of the Strategic Plan for the Prevention and Control of HIV Infection and STIs in Spain (2021-2030)[46] of the Division of HIV, STI, Viral Hepatitis and Tuberculosis Control, which also incorporates it as a second Strategic Objective (2. Promote early diagnosis of HIV infection and other STIs).[47]

As seen, diversification of STI screening and diagnosis must involve meaningful community engagement for the combined prevention package to be effective and to achieve the 2030 strategic goals.

2.3.5.2 Regulations for rapid testing in Spain in community settings

If we look at the relevant legislation, in the case of the rapid HIV test, the provisions of articles 3 and 13 of Royal Decree 1662/2000, on medical devices for "in vitro" diagnosis, which defines a "self-testing" product as any product intended by the manufacturer to be used by laypersons at home, while allowing sale and distribution in pharmacies on an individual basis and on demand to be used outside a health centre, are applicable.[18] The only self-test authorised in Spain is the HIV test. The HIV self-tests available in Spain are:

- Oraquick HIV (Self-diagnosis) [OraSure Technologies]
- INSTI HIV Self-Test (capillary blood) [Biolytical]
- HIV self test (capillary blood) [Viatris]

For the performance of rapid tests other than HIV tests not classified as self-testing products (in practice, the rest of the STI rapid diagnostic tests), the general rules on the place where such tests are to be performed are set out in Royal Decree 1277/2003, on the authorisation of health centres, services and establishments.

Despite the options for implementing HIV and other STI screening in the community setting, there are numerous legal and administrative barriers to its recommended practice. The Ministry of Health and the community response network continue to work to professionalise and train community resources and to legally protect their framework for action, in order to facilitate the development of screening for sexually transmitted infections, as well as other services related to diagnosis.

Although testing in community settings is implemented in most of the country under the state legal framework, some Autonomous Communities expand the portfolio of tests and devices for HIV and other STI screening according to their regional strategic plans and specific early diagnosis programmes, which include the participation of the community, under the framework of regional legislation. The development and use of these tests in the community setting is subject to control, monitoring and registration by the administration, requiring at least one health point of reference in each entity, who guarantees good practice in sample-taking in compliance with legislation, as well as, in most cases, specific and demonstrable training and qualification for inclusion in the community entities subject to the early diagnosis programme.

2.3.5.3 Diagnosis

STI screening would be done through self-testing devices and, in some cases, through self-collection, for infections such as viral hepatitis or syphilis.

The most common types of test are:

- Oraquick HepC (Oral fluid)
- *INSTI Multiplex HIV-1 / HIV-2 / Syphilis Antibody Test* (Capillary blood)

In some community-based checkpoint models, their health centre format within a hospital setting enables the development not only of screening for HIV and some STIs, but also the diagnosis of other infections using molecular biology techniques, as well as access to the necessary treatment.

With the rise of STIs, and recent situations such as the COVID-19 pandemic, STI testing has increased in community settings, showing through different experiences the appropriateness of implementing a broader portfolio of STI testing services in community settings and the institutional, legal and resource support for compliance.

2.3.5.4 Referral circuits

There is no global regulation or protocol determining the referral circuits between community resources and the public health system. Over the years, these referrals have been made through agreements, often informal, without a contract or framework agreement, between the two parties, facilitating access to a confirmatory diagnosis and specific treatment as soon as possible. The main circuits and spaces for coordination and referral from the community setting in relation to HIV and other STI screening are:

- Centres specialised in dealing with STIs
- Infectious diseases / HIV Units of the Hospitals in the area covered by the community resource
- Primary Care

In addition to these elements of the health system, community resources are coordinated with other key centres in the response to HIV and other STIs, such as addiction centres, social services, mental health, prisons and other social entities related to communities and the infections themselves.

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CHAPTER 3

SYNDROMIC CHAPTERS

3. Syndromic chapters

3.1 Diseases mainly represented by urethritis and cervicitis.

KEY MESSAGES

1. STIs are the main infectious cause of urethritis and cervicitis, with *N. gonorrhoeae*, *C. trachomatis* and *M. genitalium* being the most common aetiological agents .

2. Urethritis may present with urethral discharge, dysuria, increased frequency of urination and/or urethral pruritus. **Cervicitis** may be characterised by abnormal vaginal discharge, intermenstrual vaginal bleeding, abdominal pain and/or dyspareunia, although it is usually asymptomatic in most cases.

3. CT is the most prevalent bacterial STI in Spain, affecting men and women almost equally. NG is the second most common bacterial STI and mainly affects men with a median age of 30 years.

4. NAATs are the gold standard for diagnosis, with high sensitivity and specificity.

5. A culture is necessary if gonococcal infection is suspected, as it allows the isolation of the microorganism for subsequent antimicrobial susceptibility testing.

6. The recommended empirical treatment for urethritis and cervicitis is ceftriaxone 500 mg as a single dose and doxycycline 100 mg every 12 h for 7 days.

7. The recommended treatment for uncomplicated gonococcal infections is ceftriaxone 500 mg as a single dose.

8. The recommended treatment for uncomplicated CT infections is doxycycline 100 mg every 12h for 7 days.

9. The recommended treatment for MG infections depends on sensitivity to macrolides. If there is no resistance to macrolides or it is unknown: Doxycycline 100 mg every 12 hours for 7 days, followed by azithromycin 1 g as a single dose, then 500 mg daily for 3 days. If there is resistance to macrolides or failure, moxifloxacin 400 mg daily for 7 days.

10. In all persons with NG, CT or MG infection, it is recommended to complete screening for other STIs based on sexual practices and to perform the corresponding contact study.

3.1.1 General

3.1.1.1 Urethritis

It is defined by urethral inflammation and is the most common genitourinary syndrome in sexually active people with male genitalia under the age of 50.

Aetiology.

It can be non-infectious or infectious. Non-infectious causes include: chemicals/irritants (spermicides, bath/personal hygiene products, lubricants, tea tree oil, etc.), iatrogenic causes (catheterisation, instrumentation), presence of foreign bodies, endourethral neoplasia and contact dermatitis, among others. STIs are the main infectious cause, with co-infection by several agents being frequent and mainly involving *Neisseria gonorrhoeae* (10-20% of urethritis), *Chlamydia trachomatis* (15-40% of Nongonococcal urethritis (NGU)) and *Mycoplasma genitalium* (15-25% of NGU). Other less common agents are described in section 3.1.5 (Other agents).[1-6]

Clinical manifestations.

It is typically characterised by the presence of any of the following signs/symptoms: mucous, mucopurulent or purulent urethral discharge (60-90%); dysuria (50-80%), increased frequency of urination (6%) and/or intraurethral pruritus (5%), with asymptomatic cases also occurring.[1-7] Gonococcal urethritis (GU) has an incubation period of 3 to 7 days and usually presents with profuse purulent and yellowish discharge with an intense sensation of dysuria. NGU usually has a longer incubation period (2-3 weeks) and a less intense clinical manifestation (scanty mucous or mucopurulent discharge and/or dysuria) [1,2].

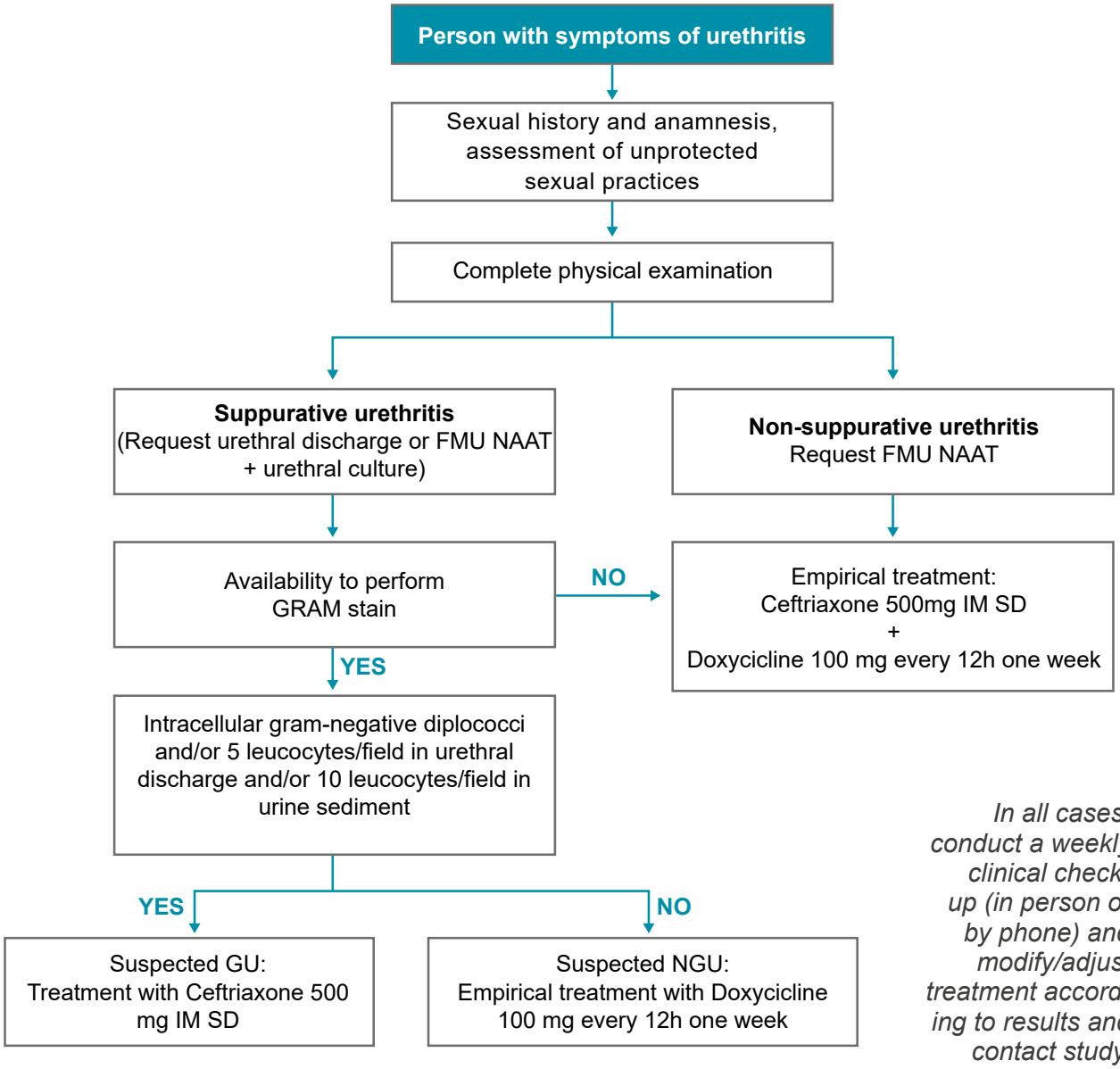
Complications.

Reactive arthritis, orchitis, epididymitis, orchiepididdymitis, prostatitis and even infertility. [1,3,5].

Diagnosis.

The orientation should be clinical. The preferred diagnostic techniques are NAAT on first morning urine (FMU) (non-suppurative urethritis; no more than 10 mL and after at least 2h urine retention) and/or NAAT and culture of urethral exudate (suppurative urethritis). Culture is especially important in the case of gonococcus prior to treatment for antibiograms and antibiotic resistance studies.[1-5]

Fig. 1: Algorithm for the initial management of urethritis



Empirical treatment.

When GU is diagnosed, Ceftriaxone 500mg intramuscular (IM) as a single dose (SD) is recommended (I-C) [1-5]. In NGU, it is recommended to start doxycycline 100mg every 12h for 7 days PO (**I-A**). It is important to note that azithromycin 1g PO SD (**III-C**) should not be used because of the increased risk of inducing MG resistance to macrolides [2–4].

If unable to differentiate between GU and NGU, treatment with both antibiotics is recommended as empirical treatment.

In addition to treatment, sexual rest is recommended for one week or until treatment is completed, as well as a contact study. The traceability period for sexual contacts is four weeks in symptomatic NGU and two weeks in symptomatic GU [3-5].

Follow-up. A follow-up visit (in person or by phone) is recommended to assess clinical progress, explain results and adjust treatment if necessary. In the presence of persistent urethral symptoms, the possibility of treatment failure, probable reinfection or other causes should be assessed. CT should be performed for second-line treatments [1-5,8,9] and in all cases of symptomatic MG [10,11].

In case of recurrent NGU (recurrence of symptoms within 30-90 days post-treatment), the index case should be retraced and a new contact study should be performed [2,4,10].

3.1.1.2 Cervicitis

Cervicitis is a syndrome characterised by inflammation of the cervix.

Aetiology. Causes of cervicitis can be non-infectious (see urethritis) or infectious. The most frequent infections are caused by CT and NG. Other causes/microorganisms include TV, genital herpes (especially primary HSV-2 infection) or MG. Often no aetiological agent can be isolated after appropriate diagnostic testing (especially in people at low risk of STIs, in whom non-infectious causes must be ruled out) [3,12-14].

Clinical manifestations.

It is characterised by the presence of abnormal vaginal discharge, intermenstrual vaginal bleeding (e.g. postcoital), suprapubic pain and/or dyspareunia, although it is usually asymptomatic in most cases. Physical examination may reveal purulent or mucopurulent endocervical discharge visible in the endocervical canal (or in the cervical swab specimen) and/or cervical bleeding [1,12,13.]

Complications. Pelvic inflammatory disease, endometritis, salpingitis, ectopic pregnancy, infertility and pre-term birth.[1,3,5]

Diagnosis.

The orientation is clinical and by compatible physical examination. The diagnostic techniques of choice are NAAT on vaginal or endocervical smear and culture. HSV testing is warranted if clinically compatible (painful vesicular lesions +/- prodromal symptoms).[1,3,5]

Empirical treatment.

In the case of clinical suspicion of cervicitis, especially if there are risk factors for STIs (under 25 years of age, multiple or new sexual partners, contact with a confirmed case of STI, and/or unlikely follow-up) in our setting, it is recommended that empirical treatment with doxycycline 100mg every 12h for 7 days PO associated with ceftriaxone 500mg IM SD (given that this is an area of high prevalence of NG) be initiated (**1-C**). If considered low risk for STIs, deferred treatment could be performed

depending on the results [1,3,5,8,9]. It is important to note that screening and treatment of symptomatic or asymptomatic women for the following pathogens is not recommended: *Mycoplasma hominis*, *Ureaplasma urealyticum*, *Ureaplasma parvum* and Group B Streptococcus [3]

Follow-up.
See section on urethritis.

3.1.1.3 Sampling

Vagina.
Visualise the area by inserting a vaginal speculum without lubricant. Take the sample from the area where the exudate is most abundant. In the absence of exudate, take the sample from the posterior vaginal fornix.[15]

Cervix.
Use an unlubricated vaginal speculum to visualise the cervix. Wipe cervical mucus with a dry swab and discard it. Insert the swab 2-3 cm into the cervical canal and rotate for 5-10 seconds.[15]

Urethra.
The patient must not have urinated for at least 2 hours prior to sampling. Use thin swabs with a wire shaft. If discharge is present or appears on pressure, collect on the swab. In absence of discharge, insert 2-3 cm thin swab and rotate 5-10 seconds.[15]

For cultures, use dacron or rayon swabs with Stuart-Amies type transport medium and activated charcoal.

For nucleic acid amplification techniques (NAAT), use specific swabs and specific containers. Send the samples refrigerated (4ºC).

First-void urine (FVU).
Collect 10 ml of the first morning urine in a urine container without preservatives. Exclusively for NAAT techniques. Collection of a volume greater than 20 ml dilutes the sample and may affect the sensitivity of the studies. The patient must not have urinated for at least 2 hours prior to sampling. Send the refrigerated sample (4ºC).[15]

Considerations for special patients.
In hysterectomised individuals, collect urine sample for NAAT or vaginal swabs from the posterior fornix for culture and NAAT.[15]
In prepubertals, take the sample from the vaginal vestibule for culture and NAAT.[15]

In persons with neovagina, swabs should be collected for culture and NAAT and an FMU.[5]

When the person presents a neophallus, an FMU should be collected. If the vagina is preserved, consideration should be given to collecting vaginal swabs for culture and NAAT based on symptoms and clinical history.[5]

3.1.2 *Neisseria gonorrhoeae* infection

3.1.2.1 Epidemiology

Gonococcal infection has shown a steady increase in incidence since 2001. In 2022, 23,333 cases of gonococcal infection were reported (rate: 49.00 per 100,000 inhabitants), showing great variability by Autonomous Community. 79.9% were men, and the median age was 30 years. According to the data from the cases where information could be obtained (46.3%) the most frequent population was men who have sex with men (MSM).[16]

3.1.2.2 Diagnosis

- Microscopic examination by Gram stain. The observation at x1000 magnification of ≥ 5 PMN per field and intracellular gram-negative diplococci allows a rapid diagnosis of gonococcal urethritis with good sensitivity and specificity in cases of male urethritis. In contrast, the sensitivity of Gram staining of urethra from asymptomatic individuals, female urethral swabs, endocervical swabs, rectal and pharyngeal swabs is low, which means it is not a useful tool to rule out these infections.[15]
- NAAT. This methodology consists of the amplification of DNA or RNA sequences using various techniques, such as polymerase chain reaction (PCR), transcription-mediated amplification (TMA) and strand displacement amplification (SDA). These are currently the recommended techniques for the detection of urogenital infections in women and men with and without symptoms due to their high sensitivity and specificity, using different platforms that have CE-IVD CE.[1,7] The PCR can detect up to one microorganism per sample, while the detection threshold of the other methods is approximately 1,000 microorganisms, so the sensitivity of a NAAT depends on the technique chosen and the type of sample analysed. It is important to mention that *N. gonorrhoeae* not only causes similar symptoms to C. *trachomatis* but sometimes both infections coexist, so diagnostic tests should diagnose both pathogens.

The recommended type of sampling is the FMU in persons assigned male at birth and vaginal sampling in persons assigned female at birth (performed by a professional or self-collection as they have been found to have equal sensitivity), although more invasive procedures can also be performed by obtaining samples from the urethra or endocervix.[17] It is important to note that self-collection is not yet authorised in Spain.

The sensitivity of NAAT in urine from persons with a vagina may be 10% lower than in vaginal exudates.[15] Laboratories with a large number of samples may consider *pooling* techniques (mixing aliquots of several samples).

- Rapid *Point-of-care testing (*POCT) using NAAT. They allow rapid diagnosis and treatment of the patient using very simple technology, with good sensitivity and specificity. The techniques that have CE-IVD for urogenital samples are the *Cepheid GeneXpert CT/NG assay* and *Binx health io CT/NG assay (binx health)* for the diagnosis of *N. gonorrhoeae* and *C. trachomatis*. POCTs are currently being developed to detect resistance simultaneously with diagnosis, in fact there is already a test on the market that detects *N. gonorrhoeae* and the ciprofloxacin resistance marker gyrA S91.
- **Culture of cervical and urethral exudate**. Although culture is less sensitive than PCR, it should be performed as it is the only diagnostic test that allows for antimicrobial susceptibility studies. It is also the recommended technique in cases of persistent infection or suspected therapeutic failure. Thayer Martin selective culture medium is used and incubated at 35-37°C in a 5% CO2 atmosphere for 48 hours. Species identification is currently achieved by mass spectrometry (MALDI-TOF) or biochemical tests.[15.]

3.1.2.3. Antimicrobial resistance

Sensibility testing

The agar dilution method is considered the leading technique for the determination of the minimum inhibitory concentration (MIC), however, the antibiotic gradient strip diffusion method is an acceptable alternative for the determination of MIC as part of the laboratory routine. The medium used is GC-based agar supplemented with 1% *Clinical and Laboratory Standards Institute* approved growth medium or 1% IsovitaleX/Vitox. The disc diffusion method, on the other hand, shows more random results, mainly to differentiate sensitive isolates from those with reduced sensitivity.[15]

In recent decades, the prevalence of *N. gonorrhoeae* strains resistant to penicillin, fluoroquinolones and tetracycline, and more recently to cephalosporins and azithromycin, has increased. This scenario has generated great concern worldwide, due to the increase in cases of gonorrhoea associated with multidrug-resistant strains. At national level, the increase in azithromycin-resistant isolates in recent years is striking, and coincides with European data, although it does vary according to the area studied.[18,19]

Ceftriaxone-resistant cases have been reported sporadically in Europe (overall rate in recent years <0.2%), mainly among those travelling from the Asia-Pacific region.[18] In Spain, in a multicentre study, the percentage of resistance to ceftriaxone and cefixime remains low and stable (0.2% and 1.7%, respectively).[19]

3.1.2.4 Treatment

Indications.

Treatment is indicated in the following cases:

- Persons who present a positive culture or molecular test (NAAT) for *N. gonorrhoeae* in any sample;
- Identification of intracellular gram-negative diplococci by microscopy of a genitourinary or pharyngeal tract sample;
- Individuals whose sexual partner(s) have a positive microbiological test for *N. gonorrhoeae* and are within 14 days of risk exposure, or neonates whose mothers have confirmed *N. gonorrhoeae* infection;
- Consider empirical treatment in cases of purulent urethritis or cervicitis after samples have been collected and in cases of sexual assault.

Therapeutic regimens.

1. Recommended regimen for uncomplicated *N. gonorrhoeae* infection of the cervix, urethra, pharynx or rectum:[20-23]

- Ceftriaxone 500 mg IM, single dose**(I-A**).

*The 500 mg dose is recommended for people who weigh <150 kg. For persons weighing ≥150 kg, 1 gram should be given.

Several guidelines in our setting recommend widespread treatment with Ceftriaxone 1g IM, single dose **(I-C**).[1,3,5.] A recent study, based on a pharmacokinetic model, describes eradication at the pharyngeal level with the 1 gram dose and not with the 500 mg dose in resistant strains with MICs of 0.5-2 mg/L, although the 500 mg dose would be effective in sensitive strains (EUCAST R cut-off point >0.125 mg/L).[71] However, in Spain, the MIC values observed in the isolates are mostly far from the cut-off point (97-99% <0.064 mg/L).[19] To date, the few resistant strains described have MIC values <0.5 mg/L and no differences have been detected depending on the anatomical site of infection. Although the pharmacokinetics of cephalosporins in the pharynx may require more time than in the genital area to eliminate the infection, the 500 mg dose of ceftriaxone in *N. gonorrhoeae* strains isolated in our country would achieve sufficient levels above the MIC values observed during the time necessary for eradication, and no therapeutic failures have been described. It is essential to maintain epidemiological surveillance and to modify the recommendation if necessary in the light of emerging evidence and epidemiological trends..

If concomitant *C. trachomatis* infection has not been ruled out, it is recommended that doxycycline 100 mg be added PO every 12 hours for 7 days[24] in addition.

2. Recommended regimens for complicated *N. gonorrhoeae* infection:

a. Pelvic inflammatory disease

- Ceftriaxone 1 gram IM, single dose + antibiotic regimen chosen to treat PID.

b. Gonococcal conjunctivitis

- Ceftriaxone 1 gram IM, single dose**(I-C**).[26]

c. Arthritis-dermatitis syndrome

- Ceftriaxone 1 gram IM or IV every 24 hours.
- Cefotaxime 1 gram IV every 8 hours.

If clinical improvement is observed, after 24-48 hours, switch to an oral regimen based on the antibiogram results, to complete at least 7 days of treatment.

Disseminated gonococcal infection.

- Ceftriaxone 1 gram IM or IV every 24 hours.
- Cefotaxime 1 gram IV every 8 hours.

If clinical improvement is observed, a switch to an oral regimen can be made after 24-48 hours based on antibiogram results, for a total of at least 7-14 days. In cases of disseminated gonococcal infection, consultation with an Infectious Diseases specialist is recommended.

Second line.

Therapeutic alternatives to ceftriaxone should be considered only in cases of penicillin allergy, contraindication to parenteral administration or any other absolute contraindication to this drug. The risk of cross-reactivity is highest with the use of first generation cephalosporins and low (<1%) with the use of third generation cephalosporins (e.g. ceftriaxone, cefixime).

The following therapeutic options are considered accepted alternatives:

1. Cefixime 800 mg orally, single dose PO, single dose (**I-B**)[27]
   Consider use only in case of contraindication to the parenteral administration.
2. Gentamicin 240 mg IM, single dose + azithromycin 2 grams PO, single dose **(I-B**)[21]
   Consider use in case of high suspicion of penicillin allergy.
3. Ciprofloxacin 500 mg PO, single dose, where sensitivity to quinolones **(I-A**) identified.[28,29]

Consider use only if quinolone susceptibility testing is available (57.7% of resistant isolates in 2020).

Pharyngeal infections are an important source of community transmission and antibiotic resistance. Although they are not usually accompanied by complications, they are more difficult to eradicate than at other anatomical locations.[25] However, no antibiotic regimen has been shown to be more effective than ceftriaxone.

Suspected therapeutic failure.
Therapeutic failure should be suspected in case of persistence of symptoms 5 days after treatment or if there is a positive test of cure (TOC) (culture or NAAT) performed at least 14 days after the end of treatment, provided that there is no documented possibility of reinfection. While most suspected treatment failures are actually reinfections, in cases of high suspicion of treatment failure it is advisable to re-collect samples for culture (and NAAT at the same time) before re-treatment. It is advisable to request a resistance test if *N. gonorrhoeae*is isolated. Re-treatment with the same regimen and a new test of cure is recommended.

3.1.2.5 Special populations

Pregnancy and breastfeeding.
Quinolones and tetracyclines are contraindicated during pregnancy and lactation. Gentamicin should be used with caution due to the potential risk of otic and renal toxicity. Ceftriaxone is recommended as the first therapeutic option (**I-A**)[31,32.]Azithromycin can be used as an alternative in patients in whom the indication for ceftriaxone is contraindicated (**I-B**).

People living with HIV.
Use the same regimens as patients without HIV infection.

Paediatric and adolescent population. [3,33]
Although the incidence rate of NG is higher in males than in females in all age groups, this difference is minimal in adolescents aged 15-19.[16]

Treatment should be adjusted according to the weight and location of the infection:

a. Uncomplicated gonococcal infection (vulvovaginitis, cervicitis, urethritis, pharyngitis or proctitis)
   - In children < 45kg: Ceftriaxone 25-50 mg/kg (max 250 mg) IV or IM single dose. In neonates (e.g. where their mothers have presented *N. gonorrhoeae* infection): maximum dose 125 mg.
   - In case of allergy to cephalosporins or contraindication to the parenteral route, consult a paediatric infectious disease specialist
   - In children > 45kg: Ceftriaxone 500 mg IM single dose.
   - Allergy to cephalosporins: Gentamicin 240 mg IM + azithromycin 2 g orally, single dose.

- Alternative: Cefixime 400 mg orally + azithromycin 2 g orally, in single doses.

b. In case of conjunctivitis: ceftriaxone 1 g, IM single dose.

c. Disseminated gonococcal infection (arthritis or bacteraemia): Ceftriaxone 50 mg/kg (maximum dose: 1 g) IM or IV as a single daily dose or other broad-spectrum cephalosporin for 7 days. In case of meningitis, extend treatment duration up to 10-14 days.

Table 1. Summary of NG drug treatments

	Of choice	Alternative
Uncomplicated infection	Ceftriaxone 500 mg SD IM.	● Gentamicin 240 mg SD IM + azithromycin 2 g SD PO ● Cefixime 800 mg SD PO ● Ciprofloxacin 500 mg SD PO (if known sensitivity)
Complicated infection*	● Pelvic inflammatory disease -Ceftriaxone 1 g SD IM + the antibiotic regimen chosen for PID. ● Gonococcal conjunctivitis -Ceftriaxone 1 SD IM ● Arthritis-dermatitis syndrome -Ceftriaxone 1 g/24 h IM/IV or Cefotaxime 1 g/8h IV. ● Endocarditis and meningitis -Ceftriaxone 1 g/24 h IM/IV or Cefotaxime 1 g/8 h IV. ● Disseminated gonococcal infection -Ceftriaxone 1 g/24 h IM/IV -Cefotaxime 1 g/8 h IV	
Pregnancy and breastfeeding	Ceftriaxone 500 mg SD IM.	If allergy to cephalosporins or other considerations preclude treatment of choice, consultation with an Infectious Diseases specialist is recommended. Caution should be exercised with the use of gentamicin during pregnancy due to the risk of nephrotoxicity or ototoxicity.

* The duration of treatment for complicated infections will depend on the location, severity and complications

3.1.2.6 Management and prevention

General measures.

Gonococcal infection is a notifiable disease and requires case and contact control measures. In the event of a new confirmed case, it is advisable to provide full information on the characteristics of the infection, its mode of transmission, potential complications and the implications for both the patient and his or her sexual partners **(III-B**). It should include information about combination prevention strategies and recommend regular STI screening and updating of active immunisation programmes (hepatitis A, hepatitis B, HPV, Mpox) in sexually active people with different sexual partners.

Sexual abstinence is recommended for patients for at least 7 days after completion of treatment, and/or until a negative test of cure is confirmed and symptoms have disappeared **(III-B**).

Test of cure.

In cases of pharyngeal gonococcal infection, in those with persistent symptoms after clinical control or in persons treated with an alternative therapeutic regimen, a test of cure (culture or NAAT) is recommended. Available evidence on the optimal timing of a test of cure is limited, however, performing it before 14 days may increase the likelihood of false positives **(II-B**). [34] Positive results should be interpreted with caution: they may be due to treatment failure, re-infection or persistence of residual non-viable genetic material in the case of NAAT use. It is important to determine the resolution of the symptomatology and to assess the possibility of re-infection during the test of cure visit. If a molecular test is chosen as a test of cure and is positive, it is advisable to confirm by culture. If the culture is positive, it is advisable to request an antibiotic sensitivity test to rule out selection of resistance.

Managing sexual partners.

The management of sexual partners is crucial in reducing the risk of reinfection. The importance of reporting, assessing and treating, if appropriate, sexual partners who meet any of the following criteria should be emphasised:

1. Sexual partners in the 2 weeks prior to symptom onset or any sexual partner with symptoms, regardless of time, in gonococcal urethritis;
2. All sexual partners in the 60 days prior to symptom onset if the infection is from sites other than the symptomatic urethral site.

If a diagnostic test is not possible, one may consider treating sexual partners empirically with the same regimen as the index case.

3.1.3 *Mycoplasma genitalium* infection

3.1.3.1 Epidemiology

The prevalence of *M. genitalium* infection in the general population is estimated to be 3-7%[37]and is higher in men and people with other sexually transmitted infections. The risk is increased in people who are young, have multiple sexual partners, or whose partners have been diagnosed with *M. genitalium*[38] infection. Transmission occurs mainly through genito-genital and ano-genital contact, with transmission through oral sex much less likely.[39]

3.1.3.2 Diagnosis

Samples recommended for molecular detection of *M. genitalium* are the same as for *N. gonorrhoeae* and *C. trachomatis*. It should be diagnosed in persons assigned male at birth with recurrent NGU, persons assigned female at birth with recurrent cervicitis and should be considered in pelvic inflammatory disease.[17]

However, screening for *M. genitalium* infection in asymptomatic individuals is not indicated, nor is screening of extragenital specimens. Screening is only indicated in patients who have been sexual contacts of a confirmed case of *M. genitalium*infection.

The method of choice is NAAT to detect only *M. genitalium* or multiplex amplification that detects other genital pathogens, using different platforms with CE marking.[40]

3.1.3.3 Antimicrobial resistance

M. genitalium lacks a cell wall, therefore antibiotics that act on bacterial wall synthesis (beta-lactams, glycopeptides, fosfomycin) are not effective for its treatment. Macrolide resistance has been progressively increasing in Europe, with rates exceeding 50% in some countries, significantly reducing the efficacy of these antibiotics.[2,5,15,17] In Spain, published resistance rates are quite homogeneous, 36.1% in Barcelona, 36.4% in Granada, 41.1% in Zaragoza and 51.8% in Madrid.[41] Therefore, whenever possible, the presence of 23S rRNA mutations that confer resistance to them should be determined. CE marked tests are commercially available with good specificity although sensitivity varies significantly between assays.[10,40]

Quinolone resistance is associated with the S83I mutation in the *parC* gene, and its prevalence varies from 0% to 15% in the United States, but its correlation with treatment failure is inconsistent.[17] In Spain, this rate is around 10% in the different studies carried out [41].Routine quinolone resistance testing is not currently indicated in Europe due to the low prevalence of quinolone resistance, the low correlation between the presence of mutations and therapeutic failure, and the fact that there are no commercial methods with CE marking.[10]

3.1.3.4 Treatment

Indications.

Treatment is indicated:

- All symptomatic subjects with a positive molecular test (NAAT) for *M. genitalium* from any genitourinary tract specimen**(I-B**).
- Asymptomatic individuals whose sexual partner(s) are symptomatic and present a positive microbiological *test* for *M. genitalium* **(I-B**).

Doxycycline in monotherapy has a very low efficacy (30-40%), however, it has been shown to increase the eradication rate if used in combination (and in advance) with azithromycin, as it reduces the bacterial load and decreases the risk of azithromycin-mutated variants leading to therapeutic failure.[42,43.]

It is therefore recommended that a two-step treatment strategy, ideally based on prior resistance testing, be used as the preferred regimen in order to increase efficacy and reduce the risk of selection of resistance mutations.

First line.

Recommended regimen for uncomplicated *M. genitalium* infection (urethra, cervix):

- Known macrolide sensitivity or unknown sensitivity: Doxycycline 100 mg every 12 hours for 7 days. This should be followed by azithromycin 1 g as a single dose, then 500 mg daily for 3 days (2.5 g in total)**(I-B**).
- If macrolide resistance exists or if azithromycin treatment has failed: Moxifloxacin 400 mg orally once daily for 7 days**(I-B**).

Recommended regimen for urogenital infection complicated by *M. genitalium* (PID, epididymo-orchitis): Moxifloxacin 400 mg orally once daily for 14 days**(I-B**)

Regimen recommended in case of complicated *M. genitalium* infection (pelvic inflammatory disease, orchiepididymitis, etc.), previous treatment failure with azithromycin or in case of known macrolide resistance mutations:

- Moxifloxacin 400 mg orally once daily for 10-14 days**(I-B**).

Second line.

Evidence on the efficacy of other lines of therapy is scarce and patients who are not candidates for treatment with the preferred regimens should be informed.[44,45] In such cases, the use of the following drugs can be considered:[46-48]

- Doxycycline 100 mg orally every 12 hours for 14 days **(I-C**).
- Pristinamycin 1 gram every 6 hours, for 10 days (foreign drug application).
- Minocycline: 100 mg orally every 12 hours for 14 days.

Efficacy rates of the alternative guidelines are variable, ranging from 68-75%.

CONDITION	OF CHOICE
Uncomplicated *M. genitalium* infection (urethra, rectum, cervix) - Known or unknown macrolide susceptibility	Doxycycline 100 mg every 12 hours for 7 days, followed by azithromycin 1 gram orally in a single dose and then 500 mg orally every 24 hours for 3 more days (2.5 g in total)**(I-B**)
Uncomplicated *M. genitalium* infection - Macrolide resistance / Failed azithromycin treatment	Moxifloxacin 400 mg orally once daily for 7 days **(I-B**)
Urogenital infection complicated by *M. genitalium* (PID, epididymo-orchitis)	Moxifloxacin 400 mg orally once daily for 14 days **(I-B**)
Complicated *M. genitalium* infection, treatment failure with azithromycin, known macrolide resistance	Moxifloxacin 400 mg orally once daily for 10-14 days**(I-B**)
Second-line or rescue treatments	Doxycycline 100 mg orally every 12 hours for 14 days**(I-C**). Pristinamycin 1 gram every 6 hours for 10 days. Minocycline: 100 mg orally every 12 hours for 14 days

Suspected therapeutic failure.

Treatment failure should be suspected if symptoms persist after completion of therapy or if a test (culture or NAAT) remains positive 5 weeks after treatment initiation, provided there has been no documented sexual re-exposure during follow-up. Repeat sample collection and antimicrobial resistance testing are recommended.

Pregnancy and breastfeeding.

M. genitalium may increase the risk of miscarriage and pre-term delivery.[49] Treatment with azithromycin (1 g on the first day followed by 500 mg for 3 more days) is considered safe and effective during pregnancy, while quinolones and tetracyclines are contraindicated during pregnancy and lactation. In cases of macrolide resistance or treatment failure with azithromycin, it is recommended to discuss thoroughly with the patient the risk-benefit balance of using alternative therapies and to consider, if appropriate, delaying treatment until after the end of pregnancy, as well as an assessment by an expert in Infectious Diseases. The use of short regimens of azithromycin during lactation is considered safe, although low levels of azithromycin may be detected in breast milk. Close monitoring of the newborn for potential adverse effects associated with the use of macrolides, such as gastrointestinal disturbances or candidiasis, is recommended.

HIV infection.

Use the same regimens as patients without HIV infection.

Paediatric and adolescent population.

There are no specific recommendations for the treatment of *M. genitalium* in the paediatric population. However, it must be borne in mind:

- Moxifloxacin is not approved for use in children under 18 years of age.
- A resistance study should be carried out and adjusted according to the antibiogram if available. If not available, it is recommended to consult an expert in paediatric infectious diseases to optimise treatment.

3.1.3.6 Management and prevention

General measures.

Comprehensive information on the characteristics of the infection, its mode of transmission, potential complications and implications for both the patient and sexual partners is advised **(III-B**). It should include information about combination prevention strategies and recommend regular STI screening and updating of active immunisation programmes (hepatitis A, hepatitis B, HPV, Mpox) in sexually active people with different sexual partners.

Sexual abstinence is recommended for patients for at least 14 days after completion of treatment, and/or a negative test of cure is available and symptoms have disappeared **(III-B**).

Test of cure.

Routine test of cure is not recommended in asymptomatic individuals treated with a recommended regimen. In settings where testing for M. genitalium is available, persons with persistent symptomatology, and in whom *M. genitalium*is detected, should be treated according to the treatments referred to above.

Although the optimal time interval to avoid false positives is not well established, it is recommended not to perform the test of cure before 3 weeks after the end of treatment **(III-B**).[50] Persistence of *M. genitalium* in a test of cure is associated with selection for antimicrobial resistance, especially if macrolides or quinolones have been used for treatment.[51] Resistance selection is less frequent if doxycycline has been used prior to the preferred regimens. Positive results should be interpreted with caution and assessed in the clinical context: they may be due to treatment failure, re-infection or persistence of residual non-viable genetic material. It is important to determine the resolution of symptomatology and to assess the possibility of re-infection during the CT visit.

Managing sexual partners.

Recent studies have shown a high prevalence of *M. genitalium* among sexual partners.[52] The management of sexual partners is therefore crucial in reducing the risk of reinfection. It is recommended that recent sexual partners of symptomatic patients be notified of the diagnosis and evaluated for diagnostic testing and treatment if positive. If a diagnostic test is not possible, one may consider treating sexual partners empirically with the same regimen as the index case.

3.1.4 *Chlamydia trachomatis* infection

3.1.4.1 Epidemiology

Anogenital and pharyngeal *Chlamydia trachomatis* infection is caused by serotypes D-K, while serotypes L1-L3 cause Lymphogranuloma venereum and acute proctitis.[53]

Anogenital infections occur as proctitis, urethritis and cervicitis. The main complications described are orchitis, orchiepididymitis, prostatitis, salpingitis, endometritis, pelvic inflammatory disease, infertility, perihepatitis and reactive arthritis. Many CT infections are asymptomatic, making early diagnosis and timely treatment difficult.[53]

According to recent reports, CT infection is the most reported curable bacterial infection in Spain.[16]

In Spain in 2022, a total of 26,518 cases were been reported (rate of 62.38 cases per 100,000 inhabitants), with an increase in rates since 2016 ((CAP: 19.3% (IC95%: 10.9; 31.3)). 48.2% were female; the ratio of cis-male/cis-female was 1.1, with a median age at diagnosis of 27 years (RIC 22-35), with cis-females being younger than cis-males (24 years (RIC: 20-30) and 30 years (RIC: 25-38), respectively).[16]

3.1.4.2 Diagnosis

As an obligate intracellular bacterium, NAATs are the method of choice. POC techniques are available on the market that allow diagnosis in 15-30 minutes, and targeted treatment can be prescribed at the same time.

3.1.4.3 Antimicrobial resistance

Determination of antimicrobial susceptibility in CT is complex, as cell culture is required. There is currently no standardised method and the techniques used are time-consuming and laborious and are therefore only performed in highly specialised laboratories.[54]

Although treatment with macrolides and tetracyclines is effective, an increase in treatment failure rates has been detected, ranging from 5 to 23%.[17,54] Most of these treatment failures are mainly due to reinfection, non-adherence to treatment or inadequate treatment. Still, sporadic cases with decreased sensitivity or resistance to macrolides or tetracyclines have been described.[55,56] Resistance mechanisms described include mutations in conserved regions of 23S rRNA genes, horizontal transfer of resistance genes and nucleotide substitution.

3.1.4.4 Treatment

The treatment of choice for both urethritis, proctitis and cervicitis due to CT D-K is doxycycline 100 mg/12h for 7 days. Azithromycin 1g PO SD could be used as an alternative treatment, particularly if there are contraindications to doxycycline, although a meta-analysis evaluating treatment for urogenital CT found that azithromycin was associated with more therapeutic failures compared to doxycycline in people with male genitalia.[9,57]

Table 3 summarises therapeutic options and levels of scientific evidence.[2,3,8,9]

Table 3. Drug treatments for urogenital CT infection

Processing
Treatment of choice (I-A) Doxycycline 100 mg c/12h for 7 days (14 days in case of orchiepididymitis)
Alternative treatment (I-A) Azithromycin 1g PO SD.
Other available options Levofloxacin 500 mg c/24h for 7 days. (CDC, IUSTI; II, B) Erythromycin 500 mg c/12h for 7 days. (II, B)

3.1.4.5 Special populations

Pregnancy and breastfeeding.

Pregnant women should be informed of the limited evidence available in this scenario. Quinolones and tetracyclines are contraindicated during pregnancy and lactation. Azithromycin treatment (1 g on the first day followed by 500 mg 2 more days, total 2 g) is considered safe and effective during pregnancy**(I-B**).[58,59] Alternatively, amoxicillin (500 mg 3 times daily for 7 days) can be used, although some in vitro models suggest that the organism may persist after administration**(I-B**). While the efficacy of erythromycin has been found to be similar to azithromycin in some studies, the high frequency of gastrointestinal adverse effects and the high likelihood of associated poor adherence means that this regimen is not recommended.[60-62] The use of short regimens of azithromycin during lactation is safe, although low levels of azithromycin may be detected in breast milk. Monitoring of the newborn is recommended to assess potential adverse effects associated with the use of macrolides, such as gastrointestinal disturbances or candidiasis.

HIV infection.
Use the same regimens as patients without HIV infection. Given the high prevalence of LGV in this population, patients with HIV and rectal *C. trachomatis* infection who have not been tested for LGV, it is recommended to extend treatment for 3 weeks and/or perform a test of cure**(III-C**).[63,64]

Paediatric and adolescent population. [3.33]
The treatment of choice should be established according to the age and weight of the patient. Potential adherence to treatment should also be assessed, as it is possible that adolescents' adherence to the 7-day treatment may be lower, and in such cases it is preferable to offer a single dose administered at the same time as the consultation. Although, as mentioned above, this means that subsequent test of cure (TOC) is mandatory.

In children and adolescents > 45 kg:

- If > 8 years: doxycycline 100mg/12 hours, 7 days, orally.
- If < 8 years or we cannot ensure adherence (preferably administered during consultation, DOT): azithromycin 1g, single dose, orally

In children < 45 kg:

- Erythromycin: 50 mg/kg/day every 6 hours, 14 days, orally.
- Doxycycline can be used as an alternative, between 8-11 years: 4.4 mg/kg/day on the first day, followed by 2.2mg/kg/day (every 12/24h) on the remaining days, up to 7 days, orally.

3.1.4.6 Management and prevention

General measures.
It is advisable to provide information, preferably in writing, on the characteristics of the infection, its mode of transmission, potential complications and implications for both the patient and their sexual partners. Information on combination prevention strategies, regular STI screening and updating of active immunisation programmes (hepatitis A, hepatitis B, HPV, Mpox) in sexually active people with different sexual partners should be provided.

Sexual rest is recommended for patients until at least 7 days after completion of treatment, and/or a negative test of cure is confirmed and symptoms have disappeared (**I-B**).

Test of Cure.
Routine cure testing is not recommended for non-pregnant individuals with uncomplicated infections treated with recommended regimens. A test of cure (ideally a molecular test) may be recommended in pregnant women, when symptoms persist or when there are doubts about adherence to treatment **(III-C**). It could also be recommended in cases of rectal infection (regardless of whether or not they

have HIV infection) where LGV has not been ruled out and a prolonged three-week course of antibiotics has not been performed**(III-C**). In order to reduce the number of false positives, it is advisable not to perform a test of cure before 4 weeks after the end of treatment.[65,66] Positive results should be interpreted with caution as there is a high probability that they correspond to reinfections rather than true therapeutic failures.[35]

Managing sexual partners.

It is recommended that all sexual partners in the last 60 days since the onset of symptoms, or the most recent sexual partner regardless of the time since sexual contact, be notified of the diagnosis and evaluated for diagnostic testing.[69,70] If testing is not possible, one may consider treating sexual partners empirically with the same regimen as the index case. The risk of re-infection with *C. trachomatis* is high and unprotected sex should be avoided until both (index case and partner(s)) have been treated or have tested negative.[67]

Contacts of patients diagnosed with LGV in the last 4 weeks prior to the onset of the patient's symptoms, or in the last 3 months if asymptomatic, should be tested for CT-LGV in the rectum, pharynx, urethra and/or cervix (as appropriate). In addition, they will be treated with doxycycline 100 mg twice daily for 7 days, or an alternative regimen of equal duration (level of evidence IV, classification C).

3.1.5 Other pathogens

CERVICITIS			
Bacteria			
Aetiology	Diagnosis	Treatment	Remarks
Gardnerella vaginalis and related bacterial vaginosis	Cervical culture Microscopy	See chapter vulvovaginitis	

Fungi			
Aetiology	Diagnosis	Treatment	Remarks
Candida spp.	Cervical culture. Microscopy	See chapter vulvovaginitis	
Viruses			
Aetiology	Diagnosis	Treatment	Remarks
HSV 1 and HSV 2	PCR, Tzanck's test, cell culture, serology	See treatment in chapter Diseases characterised by ulcers	Associated with typical HSV lesions
Parasites			
Aetiology	Diagnosis	Treatment	Remarks
Trichomonas vaginalis	Vaginal PCR	Metronidazole / Tinidazole 2g SD PO	Associated with insertive vaginal sex

URETRITIS			
Bacteria			
Aetiology	Diagnosis	Treatment	Remarks
Haemophilus (for) *influenzae*	Urethral culture Gram stain (coccobacilli Gram neg)	Rule out production of beta-lactamases. Usually sensitive to ceftriaxone, fosfomycin or fluoroquinolones	Associated with insertive oral sex High macrolide resistance
Ureaplasma urealyticum	Urethral swab PCR or FVU	Doxycycline 100 mg every 12h PO Azithromycin 1g DU PO	Only treat symptomatic individuals after other causes have been ruled out.
Neisseria meningitidis	Urethral culture	Same treatment as NG	Associated with insertive oral sex
Enterobacteriaceae	Urethral culture GRAM (GNB)	According to antibiogram	Associated with insertive anal sex
MOs related to bacterial vaginosis	Urethral culture	Metronidazole / Tinidazole 2g SD PO Metronidazole 500 mg every 12 hours 7 days	Associated with insertive vaginal sex
Polymicrobial	Urethral culture	According to antibiogram	Series of isolated cases
Viruses			
Aetiology	Diagnosis	Treatment	Remarks
HSV 1 and HSV 2	PCR, Tzanck's test, cell culture, serology	See treatment in chapter Diseases characterised by ulcers	Associated with typical HSV lesions
Adenovirus	PCR, cell culture	Symptomatic	Associated with conjunctivitis
Epstein Barr Virus	PCR	Symptomatic	Associated with insertive oral sex
Parasites			
Aetiology	Diagnosis	Treatment	Remarks
Trichomonas vaginalis	Urethral PCR or FMU. Fresh microscopy	Metronidazole / Tinidazole 2g SD PO	Associated with insertive vaginal sex

3.2 Diseases characterised mainly by anogenital ulcers

KEY MESSAGES

1. The most common aetiologies of ulcerative STIs are HSV types 1 and 2, *Treponema pallidum* and *Chlamydia trachomatis* (serotypes L1, L2 and L3).

2. Not all anogenital ulcers are infectious in nature or caused by sexually transmitted microorganisms.

3. An ulcer caused by a sexually transmitted microorganism can be located in any anatomical region, both cutaneous and mucosal.

4. Physical examination and Sexual Health anamnesis are essential for a correct differential diagnosis.

5. Empirical treatment is based on physical examination and is mainly directed against herpes virus and syphilis.

6. Nucleic acid amplification-based tests (NAAT) are the techniques of choice for aetiological diagnosis.

7. Co-infections with other sexually transmitted microorganisms must be ruled out.[72-80]

3.2. 1 Definition

An ulcer is a loss of tissue continuity with epithelial loss and exposure of the dermis that heals with scarring. Ulcers may be deep or superficial and erosive, with or without the presence of preceding vesicles. They are located on the genital organs, in the perineal or anorectal region, and may be single or multiple, with or without associated inguinal lymphadenopathy.

A broad spectrum of pathologies (infectious and non-infectious) must be considered in its aetiology. Among infectious causes, STIs are considered one of the most frequent causes of ano-genital ulcers. In a simplified scheme they may be classified according to their aetiology (Table 1).

Table 1. Infectious and non-infectious aetiologies of anogenital ulcers

Sexually transmitted infectious aetiology	Non-infectious aetiology
Herpes simplex virus 1 (HSV-1) **Herpes simplex virus 2 (HSV-2)**	Acute vulvar ulcer (Lipschutz ulcer)
***Treponema pallidum* (Syphilis)**	Fixed drug eruption
***Chlamydia trachomatis*/Lymphogranuloma venereum**	Behçet Disease
Haemophilus ducreyi (Soft chancroid or chancroid)	Traumatic
Orthopoxvirus (Mpox)	News
Klebsiella granulomatis (Granuloma inguinale)	Iatrogenic

3.2.2 Epidemiology

The relative prevalence of the different infectious aetiological agents causing genital ulcers varies by geographic region and has changed over time. HSV-1 and HSV-2 are the causative agents of genital ulcers in most regions of the world (an estimated 500 million people are living with HSV-2 infection). According to CDC statistics (*Centers for Disease Control and Prevention*), 11.9% of the population aged 14-49 years is infected with HSV-2 and 47.8% with HSV-1. HSV is slightly more common in women (50.9%) than in men (45.2%) and transmission appears to be more effective from male to female than vice versa. These are followed by infections caused by *Treponema pallidum* and serovars L1, L2 and L3 of *Chlamydia trachomatis* which cause lymphogranuloma venereum. The epidemiology of the latter has seen a slight global increase, with cases initially associated with tropical areas of equatorial Africa, India and Southeast Asia. To a much lesser extent, the infectious aetiology also includes *Haemophilus ducreyi* the agent of chancroid and *Klebsiella granulomatis* the causative agent of granuloma inguinale (donovanosis). The epidemiology of *H. ducreyi* is not well described, it usually occurs in small, sporadic outbreaks and is often associated with co-infection with *Treponema pallidum* in men who have sex with men. According to the 2017 European guideline for the management of chancroid, its frequency

is decreasing worldwide with the exception of northern India and Malawi. In addition to genital ulcers, it is a causative agent of skin ulcers in tropical areas of the South Pacific, Southeast Asia and Africa. Donovanosis caused by *Klebsiella granulomatis* is considered an STI of tropical regions with sporadic cases and is endemic in India, Papua New Guinea, Guinea, South America, the Caribbean, Vietnam, Australia and South Africa.

Non-infectious causes include sexual trauma, Behçet's syndrome and some cutaneous manifestations caused by medication, among others.

In this chapter, ulcers caused by herpes virus, *Chlamydia trachomatis* (L serovars), *Klebsiella granulomatis* and *Haemophilus ducreyi* will be discussed. Because of its relevance *Treponema pallidum* (syphilis) will be discussed with in a separate chapter.

Table 2. Characteristics of Lesions by causing agent.

	Anogenital herpes.	Syphilis	CT/LGV infection	Chancroid
Incubation period	Undetermined (except in primary herpes 7-21 days)	2-6 weeks	3-12 days for ulcer	4-10 days
Initial lesion (prior to ulcer development)	Vesicle	Papule	Erosion	Papule-pustule
Number of ulcers	Multiple/ coalescent	Not always individual	Individual	Multiple
Shape	Round/polycyclical	Round or oval	Rounded	Irregular
Depth	Superficial	Protruting	Superficial	Deep excavated
Edges	Erythematous, lobulated	Well-defined, no inflammatory signs	Erythematous	Erythematous and undermined
Lesion/ulcer bed	Clean	Clean	Clean	Purulent/haemorrhagic
Base	Non-indurated	Indurada	Non-indurated	Non-indurated
Pain	Variable	No	Intense	Variable
Lymphadenopathies	Bilateral, mobile, hard and non-painful	Bilateral, mobile, hard and non-painful	Unilateral, fixed, painful and may fistulise	Unilateral, plastron, painful and may fistulise

3.2.3 Diagnosis

Diagnosis of the specific cause should be based on clinical history, physical examination and laboratory findings. Despite clinical experience, the diagnosis of genital ulcers is incorrect up to half of the times and is difficult due to the coexistence of different microorganisms. Therefore, according to WHO recommendations, whenever same-day microbiological results obtained by molecular testing, it is recommended to wait and tailor treatment to the results. However, if this option is not available, empirical treatment is recommended to ensure treatment on the day of consultation**(A-II**) guided by local epidemiology.

Good practices (A-II):

- Sexual history to assess STI risk (anamnesis).
  - Duration of condition, acute, chronic and presence of morphological changes over time. Whether it is recurrent or is the first time it appears.
  - Symptoms. An ulcer may be asymptomatic as in the case of syphilis or present local symptoms such as pain, itching, burning and sometimes accompanied by general malaise or fever.
  - Patient's sexual history, incluiding partners and sexual practices (oral, vaginal, anal), protected or unprotected sex, sexual partners in the last month and in the last six months, to ascertain the epidemiological chain and initiate contact tracing.
- Use of prescription drugs that may have been taken before or after the onset of the ulcer.
- Physical examination of the anal and genital area.
  - Anatomical location: although we refer to anogenital ulcers, other anatomical sites are also involved during sexual contact, such as the mouth, where sexually transmitted ulcers may also be found.
  - Number: single or multiple. Superficial (erosive) or deep.
  - Shape and size.
- Perform diagnostic tests for HIV, HCV, HBV and syphilis and administration of analgesia (if needed).

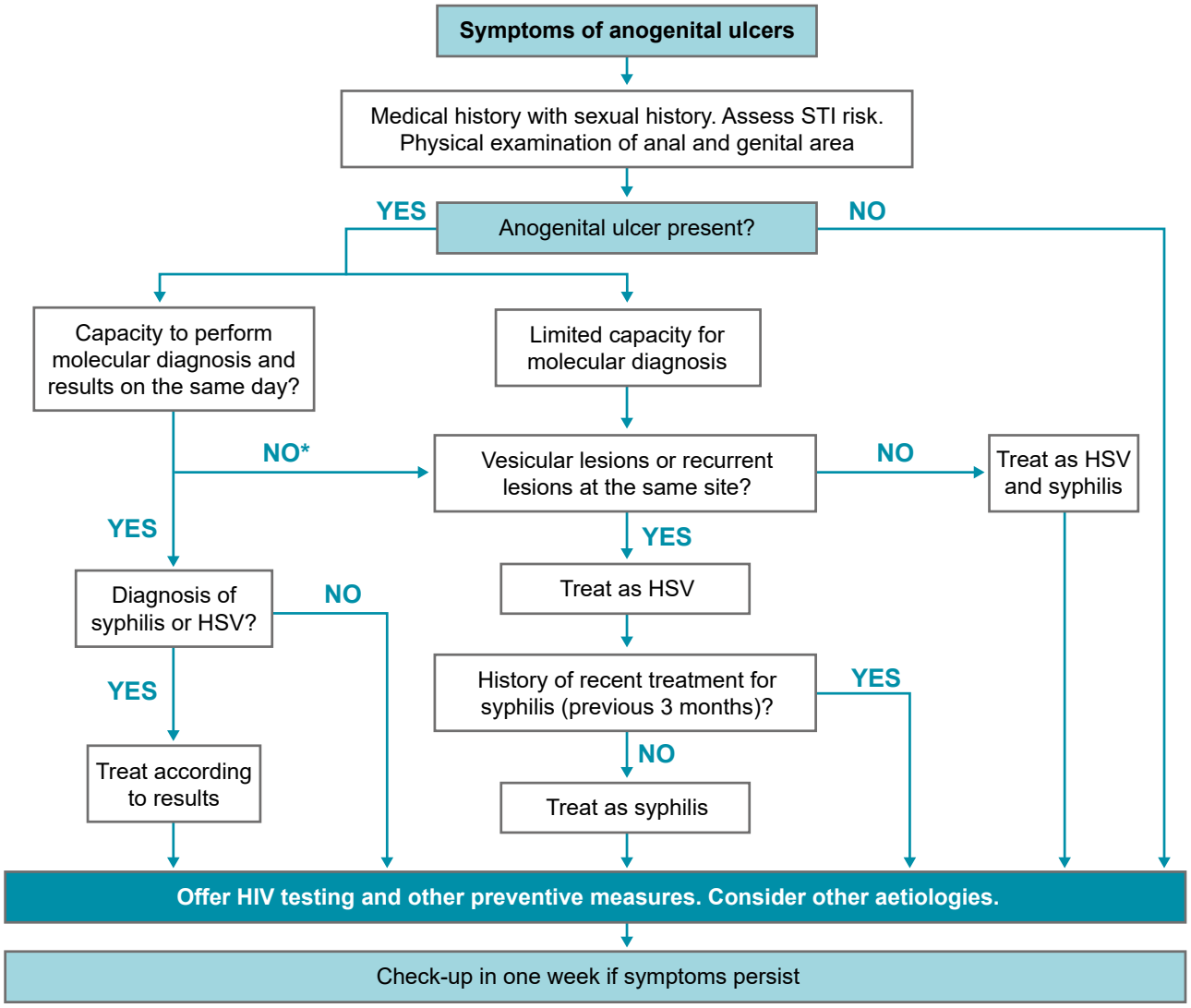
Confirmed anogenital ulcers and diagnostics availability al presentation at the time (A-II):

- Molecular diagnosis of lesions using nucleic acid amplification techniques (NAAT) of syphilis, HSV and lymphogranuloma venereum.
- Perform serological tests for syphilis and HIV.
- Treat according to results.

Confirmed anogenital ulcers with no diagnostic availability at presentation (A-II):

- Treat empirically for syphilis and HSV.
- Treat as herpes if the ulcer is recurrent, vesicular and painful.
- Refer patients with persistent anogenital ulcers to specialised centres with diagnostic capacity.

Figure 1. Diagnostic algorithm



* If molecular diagnosis is performed but results are not issued on the same day, review the syndromic treatment administered once the results are confirmed. Source: Adapted from Guidelines for the management of symptomatic sexually transmitted infections. Geneva: World Health Organization; 2021. Licence: CC BY-NC-SA 3.0 IGO and Úlceras genitales. Guías de práctica clínica MSF

3.2.4 Sampling, transport and storage of samples

For a correct diagnosis, it is necessary to take a good sample and its correct storage, transport and delivery to the microbiology laboratory.

The type of sample will depend on the patient's age, sex, sexual practices and clinical manifestations.

The sample shall be collected from an unsampled area, rotating the swab for a few seconds and always before starting antimicrobial treatment, avoiding the use of antiseptics or lubricants that inhibit or prevent the growth or detection of some microorganisms.

Table 3. Sampling by location

Location	Sampling conditions	Sample collection method	Swabs and containers	Comments
Anal/rectal.	Anoscopy (symptomatic patients).	Use unlubricated anoscope moistened with water or water-based lubricant. Take samples under direct visualisation of the lesions.	Culture: Dacron swabs with Stuart-Amies transport medium preferably with activated charcoal if NG is suspected. NAAT: specific swabs and containers.	Store at 2-8°C and send to the laboratory within 24-48 hours.
	Sampling without visual guidance.	Insert the swab 2-3 cm into the anal canal. Press laterally to avoid faecal matter and to favour the collection of columnar epithelial cells. Rotate the swab for 10-30 seconds. If visible faecal contamination is found, discard the swab and obtain a new sample.	NAAT: specific swabs and containers. Culture: dacron swabs with Stuart-Amies transport medium.	
Genital ulcer.	Wipe the surface of the lesion with a moistened gauze with sterile saline. Avoid prior application of antiseptics.	If a vesicle is present, aspirate the contents with a syringe. In the absence of vesicles, rub the base with the swab (avoiding/preventing bleeding).	NAAT: specific swabs and containers. Culture: dacron swabs with Stuart-Amies transport medium. Virus detection: virus swabs and virus transport medium (if NAAT not available) Storage at 2-8°C and shipment to the laboratory within 24-48 h (ideally within 2 h). If lymphogranuloma venereum is suspected, a puncture of the lymphadenopathy may be performed.	Storage at 2-8°C and shipment to the laboratory within 24-48 hours (ideally within 2 hours). If lymphogranuloma venereum is suspected, a puncture of the lymphadenopathy may be performed.

A summary table of diagnostic techniques is shown below:

Table 4. Diagnostic techniques by microorganism

	HSV:	Syphilis	CHANCROID	LGV	Granuloma inguinale
Direct observation.	Tzanck staining IFD.	Darkfield microscopy IFD.	Gram stain of exudate: gram-negative coccobacilli.	IFD (In disuse).	Donovan bodies inside phagocytes.
Culture.	Cell culture.	T. pallidum cannot be cultivated.	Specific non-commercial media.	No.	No.
NAAT (PCR).	Choose.	Choose. It can be helpful in diagnosis by demonstrating T. pallidum in tissue, vitreous fluid and cerebrospinal fluid (CSF) samples.	Not available in routine.	Choose.	Not available in routine.
Serology.	Only useful in primary infection.	Of choice: treponemal and non-treponemal tests. False negatives if very early diagnosis.	No.	Increased titres in two serial determinations or high titre. (In disuse).	No.

Source: Adapted from "Documento de consenso sobre diagnóstico y tratamiento de las infecciones de transmisión sexual en adultos, niños y adolescentes de GESIDA (March 2017)".

3.2.5 Anogenital herpes

3.2.5.1 Clinical classification

a) Primary herpes

Primary infection occurs when the virus (HSV-1 or 2) is acquired in the absence of prior HSV-specific immunity.

The incubation period is variable (between 2 and 14 days), and prior to the appearance of lesions there is usually a prodromal phase with systemic symptoms (fever, malaise, myalgia) and/or local symptoms such as pruritus or skin itching. Lesions begin as papules that progress to vesicle, then ulceration with complete resolution after 2-3 weeks. The lesions are often associated with pruritus or burning pain of varying intensity. Extensive and bilateral lesions are common in primary infection. Other manifestations include painful inguinal lymphadenopathy, symptoms of urethritis and the presence of leucorrhoea. HSV can also cause proctitis, when lesions are found intrarectally, with anorectal pain or itching and bleeding. In this clinical presentation of proctitis, typical perianal herpetic lesions are only present in less than half of cases. Clinical presentation with urethritis, cervicitis or proctitis is more common in primary herpes.

Possible complications include secondary infection of the lesions, and less frequently nervous system involvement with sacral radiculomyelitis leading to bladder dysfunction and urinary retention, transverse myelitis, neuralgia or aseptic meninigitis.

b) Initial non-primary herpes

Initial non-primary herpes refers to the first episode of HSV in a person with pre-existing antibodies to the virus. The clinical picture differs from that of primary infection in that both local and systemic symptoms are usually less severe and resolve more quickly.

c) Recurrent herpes

Recurrent herpes is caused by reactivation of viral replication in the spinal ganglion in response to various stimuli (stress, fever, sun exposure, immunosuppressive processes, etc.). Prodromes such as a burning or tingling sensation precede the appearance of lesions by 12-24 hours, which are usually smaller in number and extent than the initial infection. Without specific treatment they resolve after 1-2 weeks.

The frequency and intensity of recurrences are highly variable, and depend on factors such as the type of virus (more frequent for HSV-2), intensity of the first episode and host factors. Recurrences are also more frequent in the first year after infection.

d) Subclinical infection

On the one hand, primary infection is most often asymptomatic, so most patients will be unaware of their infection status. In addition, recurrences may be atypical, with the appearance of non-specific erythema, cracks or fissures, which are hardly noticeable to the patient, or even no visible lesions may develop. It should also be noted that viral shedding can occur in the absence of manifestations of recurrence.

3.2.5.2. Physical examination

The initial lesion of HSV is a maculo-papule, which rapidly evolves into a superficial vesicle of epidermal origin, with clear fluid (which may turn yellowish after a few days). This vesicle soon loses its roof, leaving a shallow, clean-bottomed ulcer. Whether we look at the vesicle or ulcer phase, we see that the lesions tend to coalesce, giving a lobulated or polycyclic appearance. Typically the lesions are multiple (although they may also be a single lesion) and are grouped on an erythematous background. Painful inguinal lymphadenopathy is frequently found, usually bilaterally in the first episodes.

3.2.5.3 Diagnostic criteria

Clinical diagnosis based on anamnesis and examination findings is sufficient to initiate empirical treatment, with the aim of reducing the intensity and duration of symptoms, but it is necessary to confirm this diagnosis a posteriori with laboratory techniques to establish the prognosis and explain to the patient the guidelines for action in the event of recurrences.

Nucleic acid amplification techniques (NAAT) are the technique of choice **(A-I**). Other less commonly used diagnostic techniques are the Tzanck smear, which is performed on an unbroken vesicle and requires experienced personnel, and viral culture, which is sensitive and specific but more complex to perform.

HSV-specific IgG anti-HSV antibody serology may be useful for patients with a history of recurrent genital ulcers in whom a PCR diagnosis has not been possible. IgM antibodies do not distinguish between acute and chronic infection and their determination is not recommended. Anti-HSV-2 IgG would be indicative of anogenital herpes, while the presence of anti-HSV-1 antibodies could not differentiate between oropharyngeal and genital infection. (**B-III**)

Serology may also be useful to guide counselling in couples with anogenital herpes. (**B-III**)

Serology is not recommended for screening in asymptomatic patients. (**B-III**)

3.2.5.4 Treatment

Acute episode.

Treatment of the first episode should be initiated within the first 5 days, or as long as new lesions appear or systemic symptoms persist. Oral antivirals are used. **(A-I**). Topicals are less effective and combined use has no additional benefit. (**C-III**). Intravenous use is only indicated when oral intake is not possible. (**B-III**)

The duration of treatment is between 5 and 10 days, the recommended guidelines are:

- Acyclovir 400 mg 3 times a day (or 200 mg 5 times a day).
- Valaciclovir 1000 mg twice daily.
- Famciclovir 250 mg 3 times a day.

The management of recurrences should be decided together with the patient, as patients with mild, self-limiting symptoms may prefer supportive care only. If treatment is started as soon as symptoms appear (even with prodromal symptoms), the benefit is greater, and an episode may even be aborted. (**B-II**)

Short regimens are preferred to 5-day regimens because they are more cost-effective, more convenient for the patient, and because there is no evidence of a difference between the two in terms of efficacy in controlling the episode. (**B-II**)

Short regimens:

- Acyclovir 800 mg three times a day for 2 days.
- Valaciclovir 500 mg twice daily for 3 days.
- Famciclovir 1 g twice daily on a single day.

Table 5.

	VALACICLOVIR	FAMCICLOVIR	ACICLOVIR	GESTATION/LACTATION
PRIMARY EPISODE	1 g oral 2 times a day for 7-10 days	250 mg oral 3 times a day for 7-10 days	400 mg oral 3 times a day for 7-10 days	ACICLOVIR 400 mg oral 3 times a day for 7-10 days
RECURRENCES	500 mg orally twice a day for 3 days O 1 g orally once a day for 5 days	1 g orally twice a day, for one day O 500 mg one day followed by 250 mg 2 times a day for 2 days O 125 mg twice a day for 5 days	800 mg twice a day for 5 days O 800 mg 3 times a day for 2 days	ACICLOVIR 800 mg 2 times a day for 5 days O ACICLOVIR 800 mg 3 times a day for 2 days
SUPPRESSIVE THERAPY	500 mg-1 g oral per day	250 mg orally twice a day	400 mg orally twice a day	ACICLOVIR 400 mg 3 times a day. O VALACICLOVIR 500 mg 2 times a day

*If symptoms persist, treatment may be extended for more than 10 days.
* Acyclovir200 mg oral 5 times a day is also effective but not recommended because of the frequency of dosing.

4 Day Regimens:

- Acyclovir 400 mg three times a day for 5 days.
- Valaciclovir 500 mg twice daily for 5 days.
- Famciclovir 125 mg twice daily for 5 days.

For patients with HIV, some authors recommend doubling the dose and/or increasing the duration of treatment (e.g. Valaciclovir 1g twice daily for 10 days), but evidence comes mostly from the pre-TARGA era. This recommendation would be particularly relevant for patients with advanced infection and low CD4 counts, whereas most patients on ART with good immunovirulatory control would respond adequately to standard guidelines. (**B-III**)

Suppressive treatment.
Suppressive treatment is recommended in patients who have 6 or more outbreaks per year. It reduces recurrences by up to 70-80% and reduces viral shedding and thus the risk of transmission. **(A-I**)

The recommended guidelines are:

- Acyclovir 400mg twice daily.
- Valaciclovir 500mg - 1 g once daily.

If suppressive treatment fails to reduce relapses, the frequency of the regimen can be increased: acyclovir 400mg 3 times a day or Valaciclovir 500 mg twice a day. (**C-III**)

Dose adjustment is only required in patients with severe renal impairment. Renal monitoring is not necessary in patients without prior pathology. (**B-III**)

Continuation of treatment should be assessed at least annually. The minimum interruption period should be 2 recurrences in order to be able to assess the severity of the recurrences. In case of persistent recurrences with significant intensity or that affect the patient's quality of life, it is advisable to restart the suppressive regimen. (**B-III**)

Supportive treatment.
Cleaning of lesions with saline is recommended. Copper and/or zinc sulphate solutions can also be used to act as an antiseptic.

Topical anaesthetics (e.g. lidocaine gel 5%) and oral analgesics can be used for pain control.

In the paediatric population, the presence of anogenital herpes always makes it necessary to investigate an episode of possible sexual violence (see Chapter 7 and 8). Treatment in acute episodes (first episode) in patients that are not able to take oral medication in tablet-form will be with acyclovir (suspension) at a dose of 80mg/kg/day, divided into four doses, every 6 hours (not to exceed adult doses of 1200mg/day). In patients that are able to take tablets, guidelines do not vary from those for adults:

Advice.
A diagnosis of genital herpes can be very stressful or emotionally upsetting for the patient. The infection should be well explained and the patient should be accompanied and any doubts that may arise should be answered. It is important to explain in detail the treatment of recurrences and to ensure that the patient will have access to medication. Suppressive treatment, if it may be necessary, should also be reported.

Regarding the possibility of transmission, sexual abstinence should be recommended during recurrences due to the increased risk of transmission, but patients should also be reminded that there is asymptomatic viral shedding, and therefore the use of barrier methods is recommended. A strategy that may also be useful is to educate the patient with few symptoms to recognise them in an attempt to limit transmission in subclinical infection.

3.2.6 Lymphogranuloma venereum

3.2.6.1 Clinical presentation

Although asymptomatic cases have been described, three successive clinical stages preceded by an incubation period ranging from 3 to 30 days are classically known:

- **Primary stage**: The primary lesion may present as a papule or pustule, a superficial erosion or a small ulcerative lesion between 1 and 6 mm in diameter. It is usually self-limiting and heals spontaneously within a few days and may go unnoticed. However, indurated lesions with variable tenderness have been reported and may persist for several weeks. The location depends on the site of inoculation, with involvement of the genital area –particularly the balanopreputial sulcus in males and the vagina, vulva or cervix in females– as well as extragenital sites, with perianal lesions or lesions in the oral cavity and tonsils.

  As a consequence of direct transmission to the rectal mucosa in receptive anal intercourse, the most frequent form of presentation in our environment is proctitis. It presents as an inflammatory bowel disease, with rectal pain, mucous and/or haemopurulent rectal discharge, tenesmus, constipation and sometimes with general symptoms and fever. (See chapter 3.4.).

- **Secondary stage**: It occurs 2-6 weeks after the primary lesion and is due to loco-regional progression of the infection. These *C. trachomatis* serovars are lymphotropic and infect lymphocytes and macrophages producing thrombolymphangitis and perilymphangitis leading to inguinal syndrome with painful lymphadenopathies (buboes), usually unilateral, with a tendency to abscessification, fistulization and spontaneous drainage. Involves inguinal and/or femoral lymph nodes. When both chains of lymphs are affected, they are separated by Poupart's inguinal ligament ("cleft sign"), which, although pathognomonic, is present in only 15-20% of cases. This may be the first clinical manifestation of infection.

  In women, groin syndrome is usually not present, as the vagina and cervix drain to deep iliac or perirectal nodes, resulting in pelvic pain or lower back pain. They are also not usually present in cases of rectal LGV. In case of pharyngeal involvement, it may present with laterocervical or submandibular lymphadenopathy.

- The **tertiary stage:** It is a consequence of persistent or progressive infection, especially in patients who have not received treatment in previous stages. A chronic inflammatory response develops, leading to destruction of the tissues in the affected areas (genito-anorectal syndrome), which presents with proctitis or proctocolitis and, in some cases, with hyperplasia of intestinal and perirectal lymphoid tissue involving the rectum and retroperitoneum, mimicking carcinoma, as well as fistulas, strictures, persistent abscesses, frozen pelvis, and infertility. Loss of lymphatic structures and poor lymphatic drainage leads to chronic oedema which can result in genital elephantiasis and may lead to widespread destruction of the external genitalia due to chronic granulomatous fibrosis ("esthiomene"). Late manifestations are more frequent in women, related to greater involvement of retroperitoneal lymph nodes.

In addition to the usual clinical forms, reactive complications with joint, cardiac, meningeal or ophthalmic involvement have been observed, albeit infrequently. Described septic complications include arthritis, pneumonitis or hepatitis, however, they occur rarely.

3.2.6.2 Treatment

Antimicrobial treatment aims to cure the infection and thus prevent the progression of tissue damage. The development of sequelae can be avoided if treatment is initiated in the early stages of infection, and it is advisable to start treatment at the time of clinical suspicion. In these cases, even if antibiotic treatment is initiated and clinical suspicion is high, other possible aetiologies must be ruled out.

- First line of treatment:

Doxycycline 100 mg every 12 hours orally for 21 days **(B-I**). In patients with persistent symptoms or in cases of severe disease, longer courses may be required.

- Alternative regimes:

Azithromycin 1 g per week for 3 weeks **(C-II**). Data available at present is inconclusive, however, it would be indicated in allergic patients, pregnant or lactating women and in other situations where doxycycline use is contraindicated.

Erythromycin 500 mg every 6 hours for 21 days **(C-II**), can be used as an alternative regimen in situations where doxycycline is contraindicated, however, high rates of side effects, especially gastrointestinal, have been reported.

Different, short regimens have been proposed with doxycycline 100 mg every 12 hours (7-14 days) but there is insufficient evidence to support its recommendation **(C-III**).

Other antimicrobials that have shown effectiveness after 3 weeks of treatment are moxifloxacin 400 mg daily**(C-II**), minocycline 300 mg first dose, followed by 200 mg every 12 hours **(C-II)**, or rifampicin 600 mg daily**(C-II**), and could be useful as a rescue regimen.

In addition to antibiotic treatment, analgesia should be prescribed for pain control. Drainage should be considered in the case of fluctuating lymphadenopathy, with needle aspiration preferred to surgical incision, which has been associated with a higher risk of fistulae. Late complications secondary to tissue fibrosis may require a reparative surgical approach, both for genitals and anal fistulae.

A test of cure should be considered in cases where symptoms persist and where a treatment alternative has been chosen (4-6 weeks after completion of antibiotic treatment).

3.2.7 Granuloma inguinale (Donovanosis)

3.2.7.1 Clinical presentation

The incubation period is not fully established, but would range from 2 weeks to 1 month. Lesions appear mostly in the genital area, and more rarely there may be involvement of the groin or other extragenital areas. Lesions begin as a subcutaneous papule or nodule that progresses to an ulcer, typically painless and friable in appearance. It is not usually accompanied by inguinal lymphadenopathy. Progression to more extensive or vegetating forms depends on factors such as susceptibility and the patients's immunity status.

3.2.7.2 Diagnosis

Confirmatory diagnosis is by visualisation of Donovan bodies in stains from smears of lesions or tissue samples obtained by biopsy. There are currently no commercially available PCRs for NAAT diagnosis, and culture is not routinely performed.

3.2.7.3 Treatment

The treatment of choice is azithromycin 1 g weekly for at least 3 weeks or until resolution of lesions. (**B-I**)

Doxycycline 100 mg or trimethoprim-sulfamethoxazole 160/800 mg every 12h for at least 21 days can be used as an alternative treatment. (**C-III**)

3.2.8 Chancroid

3.2.8.1 Clinical presentation

The incubation period is usually between 3-7 days, but can be up to 41 days. A soft erythematous papule develops at the inoculation site, which rapidly develops into a pustule and subsequently ulcerates.

It may present as an isolated lesion or multiple lesions, especially in women. They are painful, between 1 mm and 2 cm in size, not indurated with irregular undermined edges and granulomatous base with yellowish or greyish necrotic exudate, friable and bleed easily. The margins of the lesion appear inflammatory ("double Petges border"). This appearance may vary in cases of co-infection with other STIs, secondary infection, may present as giant ulcers in advanced lesions without appropriate treatment and, in many other cases, be clinically indistinguishable from syphilitic chancroid or herpes.

In males it usually affects the foreskin, balanopreputial sulcus or penile shaft. Vulvar affection (labia majora, labia minora, fork or clitoris) is most common in women, while lesions of the vagina or cervix may be asymptomatic or present with leucorrhoea or dyspareunia.

Depending on the site of inoculation, there may also be extragenital involvement with perianal or oral lesions. Cutaneous affectation (thighs or buttocks) is due to autoinoculation from the primary lesion, sometimes with opposing "kissing" lesions.

The presence of inguinal lymphadenopathy or buboes occurs 1-3 weeks after the appearance of the primary lesion. They are usually unilateral and painful, fluctuant and with a tendency to spontaneous drainage. Although characteristic, they are present in only half of the cases in males, being less frequent in women.

3.2.8.2 Diagnosis

Microbiological study would provide diagnostic certainty, but since molecular techniques are not available in all laboratories and culture is difficult, it should be considered probable, if the following criteria are met **(C-IV**):

- Presence of one or more painful ulcers.
- Lesions and lymphadenopathy - if present - have a typical appearance.
- No evidence of *T. pallidum* infection by molecular or darkfield microscopy or serology performed at least 7-14 days after the onset of the lesion.
- No evidence of HSV infection by culture or molecular techniques.

3.2.8.3 Treatment

It should be instituted upon clinical suspicion, together with appropriate analgesia for pain control.

- **First line of treatment:** Ceftriaxone 250 mg intramuscular single dose **(I,A**) or Azithromycin 1 g oral single dose **(I,A**).
- **Alternative guidelines:** Ciprofloxacin 500 mg every 12 hours orally for 3 days **(I,B**) or Erythromycin 500 mg every 6 hours orally for 7 days **(I,B**).

Improvement of the lesions is seen in the first 3-7 days, although the time to complete cure will depend on the size of the lesions, especially in more advanced cases. The possibility of therapeutic failure should be considered if there is no improvement and a different regimen should be used. In HIV patients the response is usually slower and lesions may persist in case of co-infection with untreated herpes or syphilis.

Management of fluctuant adenopathy may require drainage and is often slower to respond.

3.2.9 Other general remarks

All patients diagnosed with or suspected of any of these pathologies should receive medical-health advice explaining the risks involved in the different sexual practices and the preventive measures related to them.

Similarly, they should be given information about the pathological process and the importance of compliance with treatment to avoid the appearance of complications; of sexual abstinence until complete resolution of symptoms and completion of treatment to minimise the risk of transmission; and of informing contacts to control the chain of transmission, even if they are asymptomatic.

In addition, screening for other STIs should be performed depending on the patient's practices and include serological testing for hepatotropic viruses, as well as HIV and syphilis. Serological tests shall be repeated if window period is suspected.

Clinical follow-up is recommended until the disappearance of symptoms, evaluating clinical response, the appearance of sequelae, adequate compliance with treatment, and the appearance of side effects. As well as adequate notification of sexual partners and the possibility of re-infection.

3.3 Diseases characterised mainly by vulvovaginitis

KEY MESSAGES

1. The aim of BV treatment is to control symptoms as well as to prevent possible complications following diagnostic and/or surgical gynaecological procedures.

2. Treatment of BV in asymptomatic non-pregnant women **(**IA) is currently not recommended. Treatment should be indicated in symptomatic patients or those undergoing a gynaecological procedure**(B-II**). It could be considered in certain population groups at high risk of STIs **(IIIC**).

3. Treatment of BV is recommended for symptomatic pregnant women and asymptomatic pregnant women with risk factors for preterm birth.

4. The aetiology of *Vaginal Trichomoniasis* (VT) is almost exclusively sexually transmitted. The presence of VT in non-sexually active girls and adolescents strongly indicates sexual contact and therefore requires investigation of possible sexual violence.

5. Treatment of VT is recommended in symptomatic, asymptomatic patients and their sexual partners, and screening for the coexistence of other STIs is recommended.

6. A follow-up test, preferably with NAAT, is recommended for all sexually active women between 3 weeks and 3 months after treatment.

7. Treatment of **candidal vulvovaginitis** is indicated only in symptomatic women. Treatment of asymptomatic colonisation detected by culture or cytology is generally not recommended.

8. Systematic assessment and treatment of the sexual partner of a woman with VVC is not justified. Treatment will only be considered in cases where the sexual partner is symptomatic and in cases of treatment resistance.

3.3.1 Bacterial vaginosis

Definition:

Bacterial vaginosis (BV) is a polymicrobial disorder of the vaginal microbiome characterised by an increased load of facultative and strict anaerobic bacteria, a reduction in beneficial lactobacilli and a corresponding increase in vaginal pH.[81]

Epidemiology:

- BV is estimated to affect 23-29% of women of reproductive age, with significant variations in prevalence by geographic area (higher in South Africa and lower in Europe and Central Asia) and ethnicity (higher in black population). No differences have been reported in pregnant women compared to the general population.[81, 82]
- Risk factors: number of sexual partners, initiation of sexual activity, non-use of condoms, presence of other STIs, smoking and/or alcohol use, and douching.[81, 82]

Clinical presentation:

- It is asymptomatic in 50% of cases.
- The main clinical manifestation is white-ish or greyish leucorrhoea, adherent to the vaginal walls and with a foul odour (typically described as "rotten fish smell") [82.]
- Vulvar and urethral itching and irritation are rare (little inflammatory reaction), and when present, other causes of vulvovaginitis must be ruled out.[82]

Diagnosis:

Definitive diagnosis is established on the basis of clinical signs and characteristics of vaginal discharge, and microbiological confirmation.

Clinical diagnosis:

- Based on the criteria of Amsel et al[83] **(I-A**), suspect BV if three of the following four signs are present: (1) adherent and homogeneous greyish-white vaginal discharge; (2) vaginal pH >4.5; (3) fresh observation of key, clue or guide cells (epithelial cells with a stippled appearance due to being covered with coccobacillary bacteria); (4) fishy/amines odour after addition of 10% potassium hydroxide. It has been suggested to use only the two most objective criteria, without significant loss of sensitivity (82-100%) and specificity (93-97%): vaginal pH >4.5 and ≥ 20% key cells.[84.]
- Detection of bacterial metabolites (polyamines, short-chain fatty acids) or enzymes (proline aminopeptidase, sialidase) may also be useful **(III-C**).

Microbiological diagnosis:

- Gram stain (reference method): Microscopic observation of vaginal discharge by Gram stain. The most commonly used criterion for interpreting the results is the Nugent scoring system (**II-B**) which quantitatively assesses the abundance of the different bacterial morphotypes to give a score on the basis of which a distinction is made between normal microbiota and dysbiosis characteristic of BV. Similar results are obtained with the less complex Ison-Hay criteria (**IV-C**).
- Molecular testing: direct detection of bacterial genetic material using nucleic acid amplification methods (NAAT) or DNA probe-based techniques. The International Society for the Study of Vulvovaginal Disease (ISSVD) recommends the use of NAAT[81] **(II-B**).
- Culture. Not useful as *Gardnerella vaginalis* is part of the normal vaginal microbiota **(IV-D**).

Sample collection:

By vaginal exudate taken from the vaginal discharge or posterior vaginal fornix. Collection with dacron or nylon swab, and transported using Stuart-Amies medium or similar.[81]

Treatment:

- The aim is to control symptoms, as well as to prevent possible complications following diagnostic and/or surgical gynaecological procedures.[82]
- Treatment is currently not recommended in asymptomatic non-pregnant women **(AI**). However, screening and treatment could be considered in certain population groups at high risk for STIs, as it has been shown to be associated with HIV infection, HPV, HSV 2, *Trichomonas vaginalis*, *Chlamydia trachomatis*, *Neisseria gonorrhoeae* and *Mycoplasma genitalium*.

First-line treatments:[81]

- Patients with symptomatic BV should be treated first line with oral or topical **(IA**) metronidazole or clindamycin. Topical formulations have equal or even slightly better efficacy than oral formulations and are associated with fewer side effects and better tolerability, and are therefore often chosen as the first choice.[81, 85]
  - Metronidazole: 500mg/12h for 7 days orally or 0.75% vaginal gel, one full applicator (5 g) intravaginally, once daily for 5 days. Possible side effects are nausea, colicky abdominal pain and metallic taste, as well as disulfiram-like effect in case of alcohol intake within 24 hours after treatment.
  - Clindamycin: 2% vaginal gel, one full applicator (5 g) intravaginally, once daily for 7 days. Both drugs show cure rates of 60-90% within a month of completing treatment.

Second-line treatments:[81]

- Oral clindamycin 300 mg every 12 hours for 7 days or 100 mg vaginal ovules, one per day for 3 days. Topical application may weaken latex condoms and diaphragms within 5

days of application. Main adverse effects are gastrointestinal and vulvovaginal irritation, usually associated with candida overgrowth.

- Decualinium chloride: one 10 mg vaginal tablet, 1 tablet per day for 6 days. It has broad spectrum antimicrobial activity, both bactericidal and fungicidal, and could therefore be particularly useful in mixed infections. Possible side effects include genital itching, increased leucorrhoea or burning sensation. It does not increase the risk of candidiasis. At present, no resistance has been reported. Evidence on its efficacy in preventing recurrences is limited.[86]
- Tinidazole: 1 g orally, once daily for 5 days. Alternatively, 2 g orally once daily for 2 days can be prescribed, although the efficacy is somewhat lower and with a higher rate of side effects. Its efficacy and side effects are comparable to metronidazole.
- Probiotics: associated with pharmacological treatment may be beneficial in recurrent infections.**(IB**) In a meta-analysis, probiotics were found to decrease the rate of recurrences and the frequency of adverse effects, increasing the cure rate over antibiotics. However, there is insufficient evidence on the efficacy of probiotics as a single treatment.

Table 1. Recommended treatment guidelines for BV

FIRST-LINE TREATMENTS
Metronidazole 500mg/12h for 7 days, oral route Metronidazole gel 0.75%, 5 g, 1 application/24h x 5 days, vaginal route Clindamycin gel 2%, 5 g, 1 application/24h x 7 days, vaginal route
SECOND-LINE/ALTERNATIVE TREATMENTS
- Tinidazole 2g/24h x 2 days, orally - Tinidazole 1g/24h x 5 days, orally - Clindamycin 300mg/12h x 7 days, orally - Clindamycin vaginal ovules 100mg, 1 ovule/24h x 3 days, vaginal route - Decualinium chloride 10mg, 1 tablet/24h x 6 days, vaginal route · Probioticos

Treatment of relapses:

- Approximately 50% of women with BV will relapse within 12 months of treatment.[82]
- There is limited scientific evidence available on which treatment should be used in these cases. It is acceptable either to use the same regimen as in the initial episode or to change the active ingredient or regimen **(IIA**).
- One of the most commonly used regimens is the use of metronidazole gel 0.75% twice weekly for 4-6 months,[81] with success rates of up to 70%. It is often associated with the development of candidiasis and possible recurrence after discontinuation of treatment.
- Refractory BV is rare, and is usually associated with antibiotic resistance. It is recommended to consult an expert, change drug groups, increase doses, use multiple-dose regimens or combined therapies that combine boric acid vaginally.[88]

Management and prevention:

- Concurrent treatment of male partners should be considered in cases of recurrent and symptomatic bacterial vaginosis in women in monogamous relationships, using a combination of oral and topical antimicrobials. This recommendation is based on a randomized clinical trial that showed that treating male partners with oral metronidazole (400 mg twice daily for 7 days) plus topical 2% clindamycin cream (applied twice daily for 7 days to the glans, foreskin, and the upper part of the penis) significantly reduced recurrence, with a 12-week rate of 35% compared to 63% in the control group (absolute risk difference: −2.6 recurrences per person-year).[89]
- Treatment of female sexual partners could be considered, even in asymptomatic cases, given the high concordance rate for BV status.

Special populations

Pregnancy:

BV in pregnancy is associated with threatened preterm labour, premature rupture of membranes, chorioamnionitis, prematurity, postpartum endometritis and post-caesarean section infection.[82] Despite this, there is no agreement on the usefulness of systematic screening.

Treatment of BV is recommended for symptomatic pregnant women**(AI**) and asymptomatic pregnant women with risk factors for preterm birth**(IIB**).[82]

Topical regimens are not inferior to oral regimens:

- Metronidazole 0.75% gel intravaginally once daily for five days (one full applicator - 5 g - intravaginally, once daily for 5 days) or clindamycin cream 2% intravaginally for seven nights.[81]
- Oral metronidazole (250 mg/8h, 7 days) or clindamycin (300 mg/12h, 5-7 days).[82] Although there is no evidence on the teratogenicity of metronidazole, it is contraindicated orally in the first trimester of pregnancy.

Given the limited evidence available regarding the use of decualinium chloride in pregnant women, it should only be administered if strictly necessary and should be avoided during the 12 hours prior to birth (1 vaginal tablet daily, 6 days).

Tinidazole should be avoided.[85]

Breastfeeding:

Oral metronidazole 500 mg twice daily for seven days or metronidazole 0.75% gel 5 g once daily intravaginally for five days.[81]

It is recommended to discontinue breast-feeding during treatment and for 12-24 hours after the last dose in case of oral metronidazole, and to discontinue breast-feeding during treatment and for the following three days in case of tinidazole.[81]

Systemic exposure of lactating women to decualinium chloride is low and no harmful effects on the neonate or infant are expected, so it can be administered during lactation (one vaginal tablet daily for six days).

Immunosuppressed population:
Women living with HIV who have poorly controlled HIV infection and/or no antiretroviral therapy are at increased risk of BV. The treatment regimen in these cases is the same as for HIV-negative women.[85]

Paediatric population:
Vulvovaginitis is a common diagnosis in prepubertal girls. There are anatomical (less protection of the vaginal introitus, greater anatomical proximity to the anus), physiological (alkaline pH, atrophic mucosa) and hygienic conditions that make girls susceptible to this condition. They are generally characterised as non-specific vulvovaginitis with mixed bacterial flora, but have also been described as secondary to poor hygiene habits or the presence of local irritants, and the presence of pinworms or vaginal foreign bodies is also typical. In addition, invasion by pathogenic bacteria such as anaerobes, *Staphylococcus aureus* or *Streptococcus pyogenes* is common. However, in cases of recurrent or refractory vulvovaginitis, the presence of a sexually transmitted infection should be ruled out.

- BV is a common cause of vulvovaginitis in sexually active adolescents, however, it is rare in prepubertal girls, where sexual assault and other STIs should always be ruled out if diagnosed.
- Treatment of BV is indicated for girls and adolescents in the presence of symptoms.
- In girls, intravaginal treatment is not recommended, with the oral regimen of choice.[98]
- In girls and adolescents ≤ 45 kg, metronidazole 15 mg/kg/day (maximum 2 g/day) every 8 hours for 7 days[99] is recommended.

- In adolescents > 45 kg, the same regimen as for the adult population is recommended (table 1).

3.3.2 Vaginal trichomoniasis

Definition:

Trichomoniasis is one of the most common STIs worldwide.[90] It is caused by *Trichomonas vaginalis* (VT), an anaerobic/microaerophilic, motile, ovoid, flagellated protozoan of 10-20 µm, which colonises the human epithelium of the urogenital tract.[82]

Epidemiology:

According to data published by the WHO, the estimated prevalence of trichomoniasis in men and women is 0.6% and 5.3% respectively, with an incidence of 156 million cases worldwide.[90]

Risk Factors: Black race, adult women, low educational and socio-economic status, multiple sexual partners, smoking, HSV-2 infection. BV and infection with other STIs increases the risk of acquiring VT and its pathogenicity.[84]

Clinical picture:

It occurs asymptomatically or with mild symptoms in a high percentage of cases. Only 11-17% show typical symptoms.

Most frequent symptoms: Pruritus and frothy, yellow-green, foul-smelling, leucorrhoea are the most frequent. Vaginal pH > 4.5. They may also present with dysuria, dyspareunia, vulvar and/or vaginal erythema, strawberry cervix (pinpoint haemorrhages, observed by colposcopy in up to 90%), or pelvic pain. Symptoms often worsen during menstruation. There is no endocervical leucorrhoea, unless associated with *Chlamydia trachomatis* or *Neisseria gonorrhoeae.*[82]

Diagnosis:

- NAAT: Real-time PCR is the technique of choice with sensitivity and specificity of 89-98% and 100%, respectively**(IA**).
- Fresh examination under the microscope: Easy, quick and low cost, but with a sensitivity < 60% (specificity 100%) or lower even if the observation is delayed more than 10-30 minutes from the time of collection.
- Culture. To be completed in nutrient-rich media (Roiron or Diamond broth). Simple and low-cost, but requires 2-7 days. Sensitivity 44-75% and specificity 100%.
- Rapid tests: Based on genetic probes, immunochromatography or latex particle agglutination. Sensitivity and specificity are 40-95% and 92-100%, respectively.

Sample collection:

By vaginal exudate taken from the vaginal discharge or posterior vaginal fornix. Collection with dacron or nylon swab, and transported using Stuart-Amies medium or similar.[81]

Treatment:
The 5-nitroimidazoles (metronidazole and tinidazole) are the mainstay of treatment**(IA**).

First-line treatments:

- Metronidazole: 500mg twice daily for 7 days, orally. Alternatively, a single oral dose of 2g can be used. Results from a meta-analysis and a multicentre randomised trial[81] demonstrated the superiority of the multi-dose regimen over the single dose**(IA**). Given the lack of comparable trials in males, single-dose metronidazole is still recommended as the treatment of choice.
- Tinidazole: 2 g orally, single dose. It is considered an alternative to metronidazole.

Second-line treatments:
Alternative to 5-nitroimidazoles in cases of contraindication, allergy, or development of resistance, whose incidence is increasing (estimated between 4.3% and 10%):

- Boric acid (IIIC): rarely used and limited to vaginal formulations; it can be administered as a prolonged regimen (600 mg vaginally, twice daily for 60 days), either as monotherapy or in combination with vaginal clotrimazole.

Treatment of persistence:
The treatment regimen depends on whether or not persistence is due to re-exposure to an untreated infected sexual partner.

- In case of re-exposure: the treatment is the same as the initial treatment (7-day oral regimen).
- If no re-exposure has occurred: 2g metronidazole or tinidazole is recommended orally daily for 7 days.

Management and prevention:
A test of cure, preferably with NAAT, is recommended for all sexually active women between 3 weeks and 3 months after treatment (**IIIC**).[89]

Treatment of sexual partners is essential to prevent partner symptoms and reinfection. Sexual abstinence will be recommended until the couple has completed treatment.

Special populations:

Pregnancy:
VT can lead to pregnancy complications such as preterm labour, premature rupture of membranes or low birth weight. However, some studies question the need for routine treatment of VT in asymptomatic patients given the lack of evidence regarding the prevention of such complications.[82]

Pregnant women with symptoms should be treated with a single oral dose of 2 g metronidazole, and its use is contraindicated in the first trimester of pregnancy. Tinidazole should be avoided during pregnancy.[85]

Breastfeeding:
During breastfeeding, treatment can be with metronidazole or tinidazole, 2g orally in single doses, suspending lactation during treatment and up to 12-24 hours and 72 hours after the end of treatment for metronidazole and tinidazole respectively.[81]

Women living with HIV:
Annual screening and treatment for VT is recommended because of the high risk of pelvic inflammatory disease,[82,85] and in case of pregnancy, screening should be performed at the first antenatal visit, as VT infection is a risk factor for vertical transmission of HIV.[85]

Treatment of VT in HIV-positive women is the same as in HIV-negative women.

Paediatric population:
The presence of VT in non-sexually active girls and adolescents strongly indicates sexual contact and therefore requires investigation of a possible episode of sexual assault.

If a diagnosis of VT is made, treatment should always be initiated, regardless of the presence of symptoms.

The treatment of choice in girls and adolescents ≤ 45kg is metronidazole 15 mg/kg/day (maximum 2 g/day) every 8 hours for 7 days.[99]

- In adolescents > 45kg, metronidazole 500mg twice daily for 7 days orally is recommended. Although it is true that in adolescents in whom adherence to treatment cannot be assured, metronidazole in a single dose of 2 g orally could be considered as a first option.

3.3.3 Vulvovaginal Candidiasis

Definition:
Vulvovaginal Candidiasis VVC is a fungal infection and represents the second most frequent cause of Vulvovaginitis VV after bacterial vaginosis.[82]

Classification:

- Uncomplicated VVC: affects women without predisposing factors, such as diabetes or immunosuppressive conditions. It consists of sporadic episodes (two or less per year), with mild to moderate symptoms, and the infection is caused by *Candida albicans*. In general,

women with uncomplicated VVC will respond to any of the available treatment options. Recurrent VVC is defined as three or more confirmed cases per year.[85]

- Complicated VVC: affects women with pathologies such as diabetes, underlying immunodeficiency or requiring immunosuppressive treatment. Results in severe infection or recurrent episodes (three or more episodes in the previous year) and are due to Non-*Candida Albicans* infection.[85]

Epidemiology:

Yeasts of the genus *Candida* are part of the normal vaginal microbiota in 10-20% of women. Approximately 50% of them will suffer from vaginal candidiasis at least once in their lifetime.

80% of VVC have *Candida albicans* as the causative agent. However, in recent years the frequency of other yeasts*(Candida glabrata, C. parapsilosis, C. tropicalis, C. krusei, Saccharomyces cerevisiae*) has increased.[81]

Recurrent VVC affects an estimated 138 million women each year. The highest prevalence (9%) is between 19 and 35 years old.[93]

Risk factors associated with symptomatic VVC are: pregnancy, oestrogen contraceptives, hormonal therapies, frequent sexual intercourse and/or multiple partners, antibiotic treatment, immunosuppression and diabetes.[81]

Clinical manifestations/presentation:

- Signs and symptoms of VVC can be relatively non-specific and sometimes require differential diagnosis with other vaginal infections and vulvar dermatoses.[81,82]
- Vulvar itching, of varying intensity, is the most common symptom (90% of cases). Other possible symptoms are a burning sensation, dyspareunia and white or yellowish-white leucorrhoea (resembling yoghurt or cottage cheese). Vaginal pH remains unchanged (4-5.5).[82]
- On physical examination, women with VVC may present with inflammation of the vulvar and vaginal area, with genital erythema (sometimes discreetly scaly) of variable intensity. Satellite lesions to the vulvar or vulvoperineal lesional border, excoriations, fissures and scratching lesions secondary to pruritus[82] may be observed.

Diagnosis:

- Culture. It is the reference technique (**I-A**). Identification at species level allows better targeting of antifungal treatment, as well as resistance testing in cases of recurrent VVC.
- Microscopic examination: Fungal structures (blastospores, pseudohyphae) can be observed both in fresh and Gram-stained smears. It has low sensitivity (<60%) and specificity (<60%) and is associated with both under- and over-diagnosis.[81]

- NAAT: With high sensitivity (>90% for *C. albicans*) and specificity (>98%), it offers faster results, although its cost is higher.[81,84] Multiplex PCRs are now available that simultaneously determine bacterial vaginosis, trichomoniasis and candidiasis with high sensitivity and specificity values, although these vary between brands.[81]

Treatment:

Treatment of VVC is mainly based on azole derivatives and depends largely on the characteristics of the clinical picture (intensity of symptoms, frequency of episodes), the presence of risk factors (immunosuppression, congenital deficits, diabetes mellitus) and the type of *Candida sp.*responsible for the infection.

Treatment of asymptomatic colonisation, detected by culture or cytology, is generally not recommended.

Treatment of uncomplicated VVC:

Azole derivatives are the treatment of choice, and both local imidazole and oral triazole regimens are associated with 80-85% efficacy, with neither having been shown to be superior to the other[94] **(IA**). Both have few adverse effects at the doses used (Table 2), but potential drug interactions due to cytochrome P450 inhibition deserve special attention.

- Topical imidazoles: the most commonly used are clotrimazole and fenticonazole, although there are other drugs such as miconazole, isoconazole or econazole. They are generally well tolerated, with 1-10% associated with local adverse effects such as burning sensation. Allergic reactions are rare.
- Oral triazoles: fluconazole and itraconazole are the most commonly used oral triazoles and are an equally effective alternative to topical treatment.

Table 2. Therapeutic guidelines for the management of uncomplicated CVD

TOPICAL TREATMENT	
Clotrimazole	- Vaginal ovuli 200 mg, 1/24h x 3 days - Vaginal ovuli 100 mg, 1/12h x 7 days - Vaginal ovuli 500 mg, x 1 day - Vaginal cream 1%, 5gr, 1/24h x 7 days - Cream 1%, 1/24h x 7 days
Fenticonazole	- Vaginal ovuli 600 mg, x 1 day
ORAL TREATMENT	
Fluconazole	- 150 mg single dose, oral
Itraconazole	- 200 mg PO for 3-7 days

Treatment of complicated VVC:

Recurrent *C. albicans* VVC:
Predisposing factors should be ruled out and treated whenever possible, and a culture should be performed to determine the Candida species responsible for the clinical picture.

Induction therapy is initially used to achieve clinical remission, followed by maintenance or suppressive therapy.

- Fluconazole: 150mg/72h x 3 doses, orally, as induction therapy, then 150mg weekly for 6 months. It is the treatment of choice**(AI**), and allows good control in more than 90% of women. However, relapses are common when treatment is stopped (30-50% of cases). Topical clotrimazole and oral itraconazole can be used as an alternative to fluconazole.
- Clotrimazole: 1% vaginal cream daily for 14 days and then twice weekly for 6 months**(IA**).
- Itraconazole: 200 mg every 12 hours for 3 days orally, then 200 mg weekly thereafter**(IIIC**).

In women with intrauterine devices and chronic or recurrent VVC, device removal may be considered (**IIIC**).

Severe VVC:
For cases of VVC with very severe symptomatology, different guidelines of similar efficacy**(IIB**) could be considered:

- Azoles: topical treatment for 7 to 14 days.
- Fluconazole: 2 doses of 150 mg 72 hours apart.

***Non-albicans* and azole-resistant VVC:**
It is estimated that up to 50% of women with positive culture for *C. glabrata* are asymptomatic, so treatment is recommended only in symptomatic cases **(IIIC**).

Topical or oral azoles (other than fluconazole) are indicated for treatment of *C. glabrata* in longer courses, but given the high frequency of azole resistance, the treatment failure rate is high.

In case of azole resistance, there are different alternatives that will usually require a magistral formulation **(IIIC**), with boric acid being the most recommended option.

- Boric acid: 600 mg, 1 nightly vaginal application for 3 weeks.
- Nystatin: 100,000 units, 1 nightly vaginal application for 4 weeks.
- Amphotericin B: 50 mg, 1 nightly vaginal application for 2 weeks.

C. krusei, *C. tropicalis* and *S. cerevisiae* VVC are usually resistant to fluconazole, so treatment with topical clotrimazole (100 mg daily for two weeks), nystatin or boric acid vaginally**(IIIC**) should be recommended for symptomatic women.

Management and prevention:
Systematic assessment and treatment of the sexual partner of the woman with VVC **(IIA**) is not warranted. Treatment will only be considered in cases where the sexual partner is symptomatic and in cases of resistance to treatment.

Regarding the prevention of VVC, although in vitro data show that lactobacillus can inhibit the growth of *Candida* spp, there is insufficient evidence on the efficacy of oral or vaginal probiotics, so their use in the treatment or prevention of VVC is not currently recommended.

Special populations

Pregnancy:
Pregnancy is a known risk factor for the development of VVC, probably due to increased oestrogen levels, increased vaginal glycogen and alterations in the immune system.[81]

Treatment recommendations for VVC during pregnancy:

- Uncomplicated VVC: topical imidazoles, such as clotrimazole and miconazole, in 7-day courses. **(IA**). Oral fluconazole may be associated with malformations such as transposition of great vessels and cleft palate and also with miscarriages.[81]
- Recurrent VVC: each episode will be treated individually and the need for suppressive treatment will be assessed after delivery.
  - During pregnancy, as in the non-pregnant patient, treatment of colonisation is not indicated **(IIIA**). There is little evidence on the relationship between VVC colonisation and certain obstetric complications such as premature rupture of membranes.[82]

Breastfeeding women:
Treatment of symptomatic VVC in women breastfeeding will be similar to that of other women. Fluconazole is considered safe.

Immunosuppressed population and women living with HIV:
Women with underlying immunodeficiency, immunosuppressive therapy or poorly controlled diabetes may not have the same short-term response to treatment as immunocompetent women.[85] However, treatment of VVC in women living with HIV, including recurrent infections, does not differ from that advised for women without immunosuppression.[85]

Prophylactic suppressive treatment is not advised in the HIV-positive patient without complicated VVC, as this results in increasingly frequent replacement by fluconazole-resistant C. glabrata.[82,96]

Paediatric population:

In the paediatric population, the diagnosis of VVC should always be confirmed microbiologically before initiating treatment.

In prepubertal girls:

- Topical treatment is preferred, with clotrimazole topical cream 1% being the treatment of choice: 2-3 applications/day on lips and adjacent areas for 7-14 days.[100]
- As an alternative to topical treatment, fluconazole 150 mg, single dose, can be used.

In adolescents >12 years, the following guidelines could also be used:

- Clotrimazole cream 2% intravaginal: 1 application/day, for 3 days.
- Clotrimazole vaginal ovule 500mg: single dose in the evening.
- Clotrimazole vaginal ovule 100mg: 1 application/24h for 6-12 days.

Table 4. Diagnostic techniques by microorganism

	HSV:	Syphilis	CHANCROID
Clinical entity	Microorganisms involved	Symptomatology and Clinical Signs	Type of sample* and diagnostic method
Bacterial vaginosis.	*Gardnerella vaginalis* *Prevotella spp* *Porphyromonas spp* *Bacteroides spp* *Peptostreptococcus spp* *Mycoplasma hominis* *Ureaplasma urealyticum* *Mobiluncus spp* *Fusobacterium spp* *Atopobium vaginae*	Approximately 50% asymptomatic Exudate with 'fishy' odour Moderate homogeneous, thin, whitish-grayish vaginal discharge that adheres to the vaginal walls, pH >4.5 Absence of vaginitis	Vaginal: Gram +/- fresh or NAAT
Trichomoniasis	*Trichomonas vaginalis*	10-50% asymptomatic Pruritus, dysuria, lower abdominal pain (rare) Erythema vulvae Vaginitis Increased vaginal discharge, yellow-greenish, frothy, foul-smelling. pH>4.5	Vaginal: Fresh +/- crop or NAAT
Candidiasis	*Candida albicans* *Candida non-albicans* *Saccharomyces cerevisiae*	10-20% asymptomatic Itching, vulvar pain Odourless vaginal exudate Dyspareunia Erythema vulvae Vulvar fissures Satellite skin lesions Vulvar oedema Scant-moderate vaginal discharge, greyish-white, lumpy, odourless. pH 4-5.5	Vaginal: Fresh +/- Gram + culture or NAAT

* Neither urethral nor endocervical is recommended (the latter can be used for NAAT studies due to higher sensitivity)

3.4 Proctitis, proctocolitis and sexually transmitted enteritis

KEY MESSAGES

1. Proctitis is an inflammatory process of the rectum, primarily caused by sexually transmitted infections (STIs), which mainly affects GBMSM and can often be asymptomatic.

2. Proctocolitis and enteritis are not usually caused by STIs, although they can occasionally be transmitted by oro-anal sexual contact.

3. In case of suspected acute proctitis, it is recommended to start empirical treatment covering at least CT and NG while awaiting microbiological results.

4. If CT is detected, the presence of LGV serotypes should be investigated.

5. Screening for other STIs and screening/treatment of contacts is recommended.

3.4.1 Introduction: General approach to proctitis, proctocolitis and sexually transmitted enteritis. Algorithms for syndromic management.

Sexually transmitted infections affecting the anus, rectum, colon and small intestine involve acute or sub-acute inflammatory processes, often asymptomatic, caused by microorganisms that can be transmitted through various sexual practices such as receptive anal sex, use of contaminated sex toys, fisting or oro-anal sex. They are mostly diagnosed in MSM, with a higher prevalence in people living with HIV (PLHIV). Incidence has been increasing in recent years.[101,102]

In proctitis there is inflammation of the rectum (in the last 10-12 cm) and it is accompanied by pain, tenesmus, bleeding and discharge of mucus or pus.

In proctocolitis the inflammation goes beyond the rectum and diarrhoea and abdominal pain are added to the symptoms of proctitis. The risk is associated with receptive anal intercourse or oro-anal contact.

Enteritis affects the small intestine and manifests with diarrhoea and abdominal pain, usually without symptoms of proctitis. It may be caused by germ transmission during oro-anal contact.

Diagnostic considerations:
Most proctitis is caused by sexually transmitted infections, unlike proctocolitis and enteritis. In the differential diagnosis of proctitis, non-infectious causes such as medical radiation, inflammatory bowel disease, adverse effect of medication or trauma (some of them in a sexual context such as fisting, use of sex toys or enemas) should be considered.[101,102.]

Therefore, in the assessment of the patient with suggestive symptoms, a targeted history should be taken by asking about sexual habits **(A-III**), engagement in *chemsex*, recent travel to endemic areas and sex workers **(B-III**). A physical examination including inspection of the perianal region and conventional anoscopy/proctoscopy (if possible) or at least rectal swab sampling is recommended to obtain microbiological confirmation of the suspected diagnosis. Screening for other STIs **(A-II**) is recommended in the presence of proctitis.

Table 1 lists the main aetiological agents of each syndrome, as well as the most appropriate diagnostic techniques.

Table 1. Syndromic approach to sexually transmitted proctitis, proctocolitis and enteritis[101-107]

SYNDROME	AETIOLOGY	CLINICAL MANIFESTATIONS.	DIAGNOSIS
Proctitis	*NG; CT, serovars D-K and thosecausing LGV, L1-L3; MG; TP; HSV; CMV**2,3, Mpox* In 30-40% of cases no microorganism is identified. In 10% of cases more than one microorganism is involved	Rectal tenesmus, anorectal or suprapubic pain, mucous or purulent anal discharge, rectal bleeding, constipation. Fever and/or general malaise. It may be associated with ulcers or vesicles, oedema and erythema of the rectal mucosa. A high percentage of proctitis caused by NG and CT-DK are asymptomatic.	- Rectal swab NAAT should include detection of: CT-DK, CT-LGV-L1-L3. Additional testing for TP, HSV, and/or Mpox may be added if clinically suspected. LGV serovars (L1-L3) should be determined in all CT-positive samples **(B-II**). - Rectal exudate culture NG identification and antimicrobial susceptibility testing (**A-III**) in confirmed or suspected cases. - Anoscopy/Rectosigmoidoscopy. In selected cases of proctitis/proctocolitis and according to availability: alteration in the distal 15 cm with erythema, oedema, exudate in the lumen and/or bleeding. In LGV, friable mucosa, ulcerations and tumours can also be observed.
Proctocolitis	*Shigella spp; Campylobacter spp; Salmonella spp;* Shiga toxin-producing *Escherichia coli (STEC);* CT-LGV-L1-L3*; Clostridioides difficile**2*; Cryptosporidium spp.;* Human intestinal *spirochetosis (HIS)**4*; Entamoeba histolytica;* CMV*2,3	Clinic of proctitis; in addition: abdominal cramping pain (especially hypogastric), diarrhoea (often bloody), general symptoms (fever, chills, myalgia, vomiting).	- Stool culture. - Microscopic examination for parasites in stool. Stool NAAT for bacteria and parasites (subject to availability; highly sensitive tests. - Stool PCR for bacteria and parasites, subject to availability. These are very sensitive tests.
Enteritis	*Shigella spp; Campylobacter spp; Salmonella spp; G. lamblia spp; Crytosporidium spp**1,3 *isospora belli;**1,3 *Microsporidium spp;**2,3 *Strongyloides stercoralis;**2 *Entamoeba histolytica; Mycobacterium* avium-intracellulare;*2 CMV*2,3	Nausea, vomiting, diarrhoea, colicky abdominal pain, bloating, fever, no symptoms of proctitis or proctocolitis.	-Stool culture (for bacterial pathogens). -Microscopic examination for parasites (*G. lamblia* cysts/trophozoites). Recommendation: Three sequential stool samples (**A-III**). -Immunological tests: Fecal antigen testing (sensitivity/specificity ~100%). Immunochromatography (Giardia, Cryptosporidium, Entamoeba). Indirect immunofluorescence (**A-I**). -Stool NAAT (for bacteria/parasites, if available). -Duodenal aspirate/biopsy (selected enteritis cases). Note: Sigmoidoscopy is usually non-diagnostic.

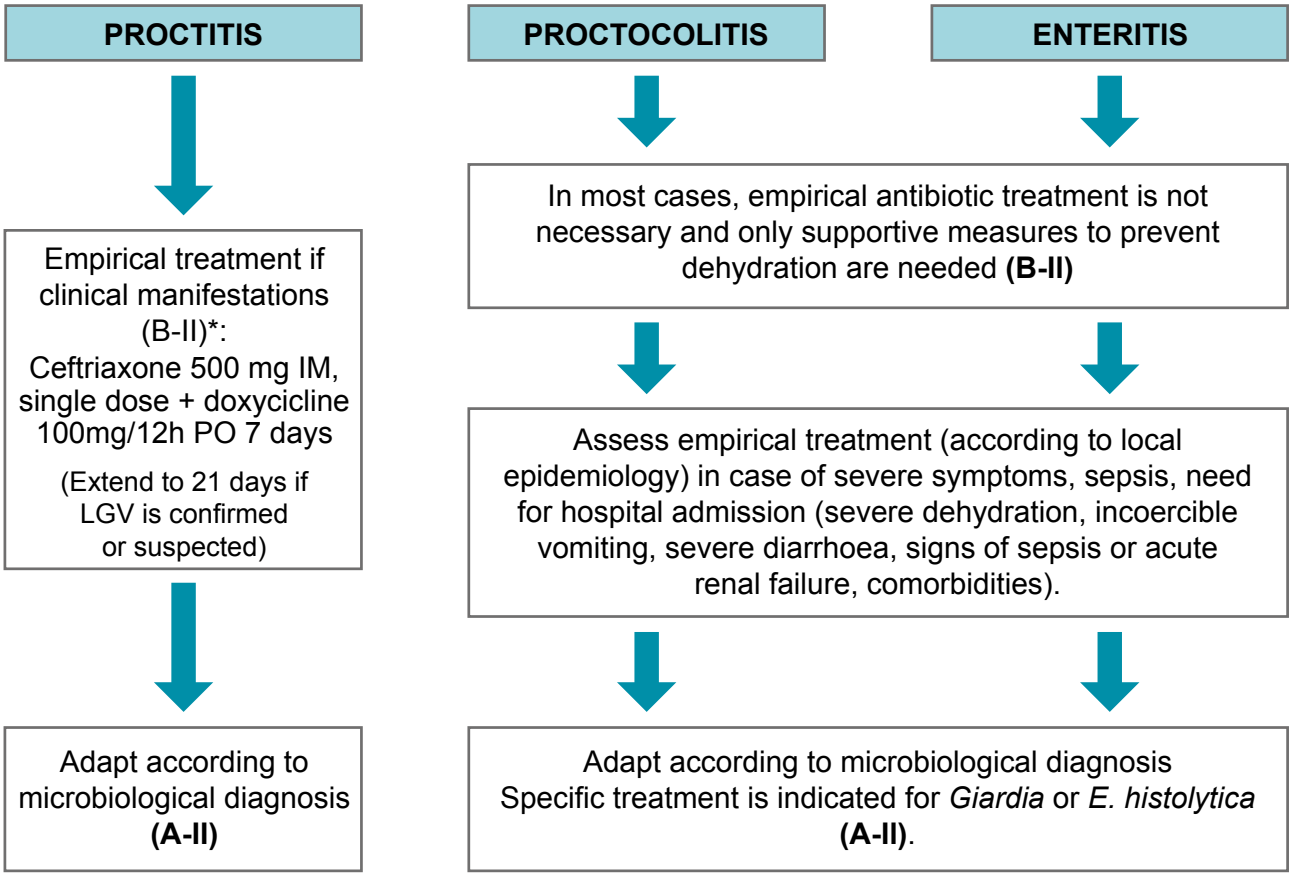
1 The role of MG in symptomatic proctitis is unclear. Consider only in the symptomatic patient with no alternative aetiology and only after other causes have been ruled out. The MG-specific NAAT test is not recommended, but if positive and available, a macrolide resistance test **(B-III) should be performed.*
**2 CMV, Clostridium difficile, Strongyloides stercoralis, Cyptosporidium spp, Microsporidium spp or Mycobacterium avium-intracellulare are not considered sexually transmitted infections, but should be considered in the differential diagnosis.*
**3 In severely immunocompromised patients, people with HIV with low CD4 counts (<200 cells/µL).*
**4 EIH may be an incidental finding in colonic biopsies in immunocompetent individuals, but can occasionally lead to opportunistic infection and associated symptomatology in the absence of other aetiologies.*

Treatment

Empirical treatment:

In case of acute clinical proctitis in persons reporting receptive anal sex, it is recommended to start empirical treatment if results are not available on the same day**(B-II**).[105] Figure 1 summarises the empirical treatment of proctitis, proctocolitis and enteritis.

Figure 1: Empirical treatment of proctitis, proctocolitis and enteritis



In case of ulcerative proctitis, consider adding treatment for herpes.

Aetiological treatment:

Whenever possible, treatment should be guided by microbiological results. Table 2 summarises the treatments of the main aetiological agents.

Table 2. Treatment of the main aetiological agents

MICROORGANISM	TREATMENT OF CHOICE	ALTERNATIVE TREATMENT
N. gonorrhoeae.	Ceftriaxone 500 mg IM, single dose.	(See other options in the corresponding chapter).
Chlamydia trachomatis serotypes D-K.	Doxycycline 100mg/12h PO 7 days **(A-I**).	Azithromycin 1g PO SD **(B-II**) (See other options in the corresponding chapter).
Chlamydia trachomatis serotypes L1-L3 (LGV).	Doxycycline 100mg/12h PO 21 days **(A-I**).	Azithromycin 1g/week PO 3 weeks (**B-II**) *1.
T. pallidum (early, primary syphilis).	Penicillin G benzathine 2,4MU IM DU**(A-I**).	Doxycycline 100mg/12h PO 2 weeks (**A-II**) Ceftriaxone 1g/d IV or IM 10 days**(B-II**).
Herpes Simplex Virus type 1 and 2.	Primoinfection: Acyclovir 400mg/8h PO 7-10 days or Valaciclovir 0.5-1g/12h PO 7-10 days or Famciclovir 250mg/8h PO 7-10 days Recurrences: Acyclovir 400mg/8h PO 3-5 days or Valaciclovir 500mg/12h PO 3-5 days or 1g/24h 5 days (See more recommended guidelines in the corresponding chapter).	
*M. genitalium.**2	The role of MG in symptomatic proctitis is unclear. Consider only in the symptomatic patient with no alternative aetiology. (See treatment recommendations in the corresponding chapter).	
Mpox	(See recommendations in the corresponding chapter).	Consider use of topical and systemic corticosteroids in case of highly inflammatory proctitis and low suspicion of another pathogen.
Intestinal amebiasis *(E. histolytica*).	Tinidazole 2g/day PO 3 days or Metronidazole 750mg/8h PO 7 days followed by Paromomycin 500mg/8h (25-35 mg/kg/day in 3 doses) PO 7 days. Asymptomatic carrier: Paromomycin 500mg/8h (25-35 mg/kg/day in 3 doses) PO 7 days.	
G. lamblia.	Tinidazole 2g PO in single dose.	Metronidazole 250mg/8h PO 5 days or Albendazole 400mg/day PO 5 days.
C. jejuni salmonella spp. (not typhi), *Shigella spp*.	In most cases, empirical antibiotic treatment is not necessary and only supportive measures to prevent dehydration are needed.	Assess antibiotic treatment (according to local epidemiology and microbiological findings) if severe symptoms, sepsis, need for hospital admission (severe dehydration, incoercible vomiting, severe diarrhoea, signs of sepsis or acute renal failure, comorbidities).

***1** If alternative treatment with azithromycin is used, it is recommended to perform a NAAT test of cure about 4 weeks after the end of treatment. ***2** Consider only in the symptomatic patient with no alternative aetiology. It is recommended to perform a healing test about 3 weeks after the end of the treatment.*

Neisseria gonorrhoeae:

Gonococcal proctitis typically presents with classic proctitis symptoms—including pain, tenesmus, bleeding, and mucopurulent discharge—due to its predominantly distal involvement in the anorectal region. However, asymptomatic anal *N. gonorrhoeae* infection is highly prevalent, with rates (66–85%) exceeding those of asymptomatic urethral infection.[101,103,109]

Gonococcal proctitis can cause different local (abscesses, fistulas or fissures) or systemic complications in the context of disseminated gonococcal infection (0.5-3%). Other infections, such as conjunctival infection, are usually due to autoinoculation, with potentially serious local involvement[101,103] (see the corresponding chapter).

Chlamydia trachomatis.

As with NG anal infection with CT is mostly asymptomatic, particularly when caused by serovars D-K, with involvement usually limited to the mucosa. In contrast, infection with L1–L3 serovars (lymphogranuloma venereum, LGV) is mostly symptomatic due to its invasive nature and ability to spread, with asymptomatic cases limited to 25%.[101,108,110]

Anorectal LGV typically presents with tenesmus, rectal bleeding, severe anal pain, a sensation of incomplete evacuation, and purulent discharge. Without treatment, progression to proctocolitis may occur, exacerbating symptoms.[101,107,108,110] Characteristically, CT infection can cause anal, perianal or rectal ulcers, with diffuse ulceration of the anorectal tract, edematous involvement (sometimes palpable as a pseudomass or tumor) and friability of the mucosa being typical of LGV, findings that are usually visible on conventional anoscopy. This pathogenesis can lead to various complications such as abscesses, fistulas, fissures and secondary strictures, the prevention of which is often facilitated by early diagnosis and treatment. Periodic screening is therefore recommended for people at high risk, primarily PLHIV (given the observed association with LGV infection), or PrEP users with multiple partners.(**A-I**)[108]

In anorectal clinic cases, palpation of inguinal adenopathies is not frequent, but involvement of the pelvic lymph node chains is common, which can lead to hypogastric or lumbosacral pain. Systemic complications are rare, with reactive arthritis being the most common.[101,108]

Anorectal LGV may mimic other forms of proctocolitis or inflammatory bowel disease. It can also occur in other locations (genital, oropharyngeal) with regional adenopathic involvement, with or without ulceration.[101,108,110]

Other pathogens

HSV 1 and 2:

HSV can cause ulcerative proctitis, usually associated with erosive, painful, superficial lesions, occasionally accompanied by bilateral inguinal lymphadenopathy, dysaesthesia/paraesthesia, malaise, myalgia or fever (see corresponding chapter).

Syphilis:

Anorectal infection with *T. pallidum* may occasionally produce ulcerative and infiltrative lesions in the anal canal or distal rectal region, which may cause proctitis symptoms (see corresponding chapter).

Other pathogens with other major routes of acquisition can also be transmitted sexually either by contact or by oro-anal transmission.

Giardiasis:

Giardia duodenalis (G. lamblia and *G. intestinalis*) is asymptomatic in 40% of cases, but may cause enteritis in the form of mild, self-limiting diarrhoea, flatulence, abdominal pain or more severe watery diarrhoea or steatorrhoea and weight loss, lasting on average 6 weeks.[102] Diagnosis is made by microscopic observation of cysts and trophozoites in stool. There are different immunological tests for its diagnosis, such as the determination of antigens in stool, with a sensitivity and specificity close to 100%, immunochromatography, and indirect immunofluorescence. The most sensitive test for diagnosis is NAAT. Treatment shortens the duration of symptoms and reduces their severity, with metronidazole**(A-I**) or tinidazole**(A-I**) the treatment of choice. Contact tracing in the previous 4 weeks is recommended only in cases of recurrent giardiasis**(A-III**).[101,102]

Shigellosis:

The *Shigella flexneri* y *Shigella sonnei* can cause proctocolitis, typically self-limiting, but may also lead to severe symptoms, including: diarrhoea, abdominal pain, nausea, vomiting, fever and rectal symptoms, lasting on average 10 days.[102] Given the frequency of epidemiological outbreaks of multidrug-resistant shigellosis, conservative management is recommended, with antibiotic therapy guided by antibiogram (**A-II**) relegated to cases of sepsis, diarrhoea lasting more than 7 days or persons with comorbidity or who are immunosuppressed (**A-II**)[102] Screening of asymptomatic contacts is not recommended (**A-III**).

Intestinal spirochetosis:

Spirochetes of the *Brachyspiraceae* family (*B. pilosicoli* and *B. aalborgi*) are associated with intestinal spirochetosis, primarily in MSM (men who have sex with men) and PLHIV (people living with HIV). While most cases involve asymptomatic colonization, these bacteria can cause opportunistic infections and chronic symptoms, including: chronic diarrhoea, abdominal pain, constipation, nausea, vomiting, rectal symptoms or even spirochetemia (especially *B. pilosicoli*).[104] Diagnosis is by exclusion by pathological confirmation in colonic biopsies by Warthin-Starry staining. The treatment of choice in symptomatic individuals is metronidazole.[101] The contact study is not necessary.

Amebiasis:

The *E. histolytica* can manifest as: proctocolitis, extraluminal complications (e.g., liver abscesses), although 90% of people remain asymptomatic. Microscopic techniques do not distinguish cysts of *E. histolytica* from some non-pathogenic amoeba species (such as *E. dispar*), so the diagnostic method of choice is NAAT (**A-II**). A contact study of the previous 3-4 months is recommended (**A-II**) and treatment in all persons with *E. histolytica* confirmed (**A-II**), the treatment of choice being tinidazole (amoebicidal agent)(**A-II**) followed by paromomycin (cyst invasion and transmission prevention agent)(**B-II**).[101,102].

Mpox:

Mpox can cause proctitis or proctocolitis, often ulcerative and severely painful, particularly in individuals practicing receptive anal sex.[111] It may be accompanied by perianal skin lesions (pseudopapules, pseudopustules or ulcerations), inguinal adenopathies and/or systemic symptoms such as fever, arthromyalgia or general malaise and lead to local complications such as bacterial superinfection, perianal abscesses, fistulas or intestinal perforation and sepsis (see corresponding chapter).

Paediatric population:

For paediatric patients weighing less than 45 kg or not taking tablets, please refer to the relevant chapters (3.1. Diseases characterised mainly by urethritis and cervicitis, 3.2. Diseases characterised mainly by anogenital ulcers, 4. Syphilis.*

3.5 Diseases characterised mainly by cutaneous manifestations

Introduction

A diverse group of dermatological disorders, these conditions can have multiple causes; whether infectious, abnormal immune responses, genetic factors or allergic reactions. Accurate diagnosis is achieved by clinical evaluation, laboratory tests and, in some cases, skin biopsies.

The management of diseases characterised by anogenital mucocutaneous manifestations is essential due to their aetiological complexity and clinical implications. In this section we offer a guide on how to deal with these injuries, which have been divided into four groups of pathologies as set out below.

KEY MESSAGES

1. **Candidal balanitis** is not considered a sexually transmitted infection.

2. **If symptoms of balanoposthitis persist or recur after 4 weeks of treatment** without a clear cause, consider a diagnostic biopsy.

3. ***Molluscipoxvirus*** **is transmitted directly by skin-to-skin contact** and can affect any location. In adults, genito/anal localisation is considered a STI.

4. Person-to-person **transmission of the mpox virus** can occur through direct contact, fomites, respiratory secretions or vertical transmission.

5. Patients with **Mpox virus transmission through sexual contact** may present with prodromal systemic symptoms followed by a characteristic skin rash starting at the site of virus inoculation (usually in the genital-anal, pharyngeal or perioral area).

6. **Pubic lice** *(Phthirus pubis*) does not transmit other infections, but may be associated with the presence of other STIs.

7. ***Sarcoptes scabiei*** **is transmitted through direct and prolonged skin-to-skin contact.** Transmission via fomites is rare in classical scabies but more likely in crusted scabies.

8. The most important manifestation of **scabies** is pruritus, which is predominantly nocturnal. It is caused by host sensitisation (type IV hypersensitivity reaction).

9. **Fixed drug eruption (FDE)** is a localised toxicoderma that frequently affects the genitalia, presenting as one or more erythematous/violaceous macules/plaques that may become eroded. Treatment consists of withdrawal of the causative drug and symptomatic measures.

10. **Lichen sclerosus (LS)** is a chronic inflammatory dermatosis that frequently affects the anogenital area. It can cause fibrosis and scarring and is at risk of malignisation to squamous cell carcinoma.

3.5.1 Balanoposthitis

Introduction:

Balanitis is an inflammatory condition affecting the glans penis and usually coexists with inflammation of the foreskin; in this case, it is referred to as balanoposthitis (BP).

Aetiology:

It is more common in uncircumcised males as the presence of the foreskin contributes to its occurrence.[112,113,114] The main aetiology is poor hygiene (non-specific balanoposthitis). Other predisposing factors include excessive hygiene, diabetes, infections, contact allergies, chronic dermatoses, application of drugs or topical cosmetics, and trauma.[114]

Infectious causes include candidiasis, syphilis, *Staphylococcus aureus*, group A streptococcus, anaerobic bacteria, *Trichomonas vaginalis* and viruses such as human papillomavirus (HPV), *Herpes simplex* virus (HSV) and Mpox.[113]

The most common inflammatory aetiologies are contact dermatitis, eczematous balanitis (seborrhoeic dermatitis, irritant dermatitis, etc.), psoriasis, lichen planus, Zoon's balanitis and lichen sclerosus.[114]

Lichen sclerosus and chronic high-risk oncogenic HPV infection carry a risk of malignancy. This includes the potential development of high-grade intraepithelial dysplasia lesions, which may progress to squamous cell carcinoma.

Epidemiology:

It affects up to 12-20% of paediatric and adult males. The highest prevalence occurs in uncircumcised diabetic males (35%). Circumcision can reduce the risk by 68%.[114]

Physical examination: Balanoposthitis presents as pain, pruritus, hypersensitivity of the glans and foreskin, accompanied by mucocutaneous lesions of variable shape depending on the specific aetiology.[113,114]

Treatment:

Treatment should be aetiological. In cases of severe phimosis with urinary obstruction, catheterisation of the urinary tract should be performed. Post-ectomy can wait for oedema reduction.

Treatment according to aetiology is presented below.

- ***Nonspecific balanoposthitis:*** correct cleaning and drying of the area 2-3 times a day. Resolution of symptoms usually occurs within several days.
- ***Irritative balanoposthitis:*** more frequent in patients with atopic context. Avoid irritating or allergenic products: detergents, latex condoms, lubricants that may be involved and

apply emollients several times a day. Hydrocortisone 1% can be added in a thin layer 1-2 weeks.[114]

- ***Candidiasis infection:*** often proper hygiene is sufficient to control the episode. If drug treatment is required, clotrimazole 1% twice/day (BID) for 7-14 days**(I-B**), or fluconazole 150 mg single dose PO in more severe cases**(I-B**) are the treatment of choice. Alternatives: topical miconazole 2% for 7 days, nystatin 100,000 u/gram 3 times/day (TID) for 2 weeks if azole resistance or allergy is suspected**(II-B**), topical imidazole with hydrocortisone 1% if relevant inflammation is present **(II-C**).[113,114]
- ***Bacterial balanoposthitis:*** mupirocin 2% TID 7-14 days in mild cases. In severe cases or with phimosis, oral route should be changed according to culture and antibiogram. If symptoms are severe, Group A Streptococcus should be covered with penicillin for 10 days **(I-B**).[113]
- ***Sexually transmitted bacterial infections:*** NG and CT can be treated with single-dose ceftriaxone 500 mg IM (except for complicated infections and weight <150 kg) and doxycycline 100mg/12h for 7 days PO. If there is a non-painful ulcer (syphilis), penicillin G 2.4 MU IM single dose**(I-A**)[114] should be administered.
- ***Anaerobic infections:*** topical metronidazole can be used in mild cases, with metronidazole PO 7 days reserved for more severe cases.
- ***Circinate balanitis:*** may occur in association with reactive arthritis. Treatment includes that of the underlying disease and topical corticosteroids (hydrocortisone 1% thin film 1-2 weeks) may be added.
- ***Viral balanoposthitis:*** see Mpox, HSV and HPV treatment in the specific chapters.
- ***Fixed drug eruption (FDE):*** The trigger drug must be stopped and avoided in the future. Hydrocortisone BID thin film can be added for 1-2 weeks **(III-C**).
- ***Lichen sclerosus (LS):*** wash with water without soap, and avoid other local irritants. Clobetasol BID for 1 month.[113] Requires maintenance treatment and follow-up due to risk of malignancy. Surgical treatment of scar sequelae.
- ***Lichen planus: avoid local irritants.*** Lubricants in case of dyspareunia. Clobetasol (**I-B**).
- ***Zoon's balanitis:*** hygiene measures**(I-B**), topical corticosteroids (topical clobetasone with nystatin and oxytetracycline 1-2 times/day), mupirocin. Post-ectomy may be required. Alternatives: Laser ablation **(III-C**).

Differential diagnosis:

Psoriatic balanitis, eczematous balanitis, lichen planus, circinate balanitis, lichen sclerosus (xerotic balanitis obliterans), fixed drug eruption, HPV, reactive arthritis. Lesions of intraepithelial dysplasia or malignant neoplasia (most frequently squamous cell carcinoma) may present with a clinical presentation very similar to balanitis.

Complications

Most patients present with mild to moderate forms with good response to specific treatment.

Biopsy will be necessary in patients with recurrent or refractory symptoms after 4 weeks**(III-B**),[114] which is usually 1 in 10. Balanoposthitis can be complicated by phimosis, scarring of the foreskin, difficulty urinating or ulcers. Refractory cases may be due to cancer, mainly squamous cell carcinoma or precancerous lesions (intraepidermal dysplasia).[113,114]

Special populations: Children and adolescents

Non-specific balanoposthitis is the most common cause in children. Candidal balanitis is prevalent in children and can be associated with nappy rash.[114]

In the paediatric population, concomitant urethral discharge or a poor clinical course warrants investigation for STIs via microbiological testing if suspected. Sexual violence must always be considered and ruled out in such cases.

The condition typically resolves with hygienic measures. For irritative causes, topical corticosteroid (hydrocortisone 1%) may be added. If bacterial infection is suspected, topical mupirocin 2% is the treatment of choice, except in cases of Group A *Streptococcus*, *S. aureus*, or anaerobe isolation, immunocompromised patients, or severe cases, where oral antibiotic therapy is recommended.

Treatments for NG, CT or syphilis infection in the paediatric population can be found in the relevant chapter.

3.5.2 Other pathogens: *(Molluscum contagiosum*, Mpox, Zika)

3.5.2.1. *Molluscum contagiosum* (MC)

Definition:

MC is a cutaneous viral infection caused by *Molluscipoxvirus*, a double-stranded DNA virus that is a member of the poxvirus[115] family. In turn, it is divided according to genotype into 4 groups, all with identical clinical presentation.

Epidemiology: Global distribution

It is the most common poxvirus infection in humans today with a prevalence of 5.1% to 11.5% in children according to different studies in Western countries and a seroprevalence of 39% in adults.[116]

Genotype 2 is the most frequent genotype associated with infections in sexually active young adults in the genito-anal area.[116]

Transmission:
MC is transmitted directly by skin-to-skin contact and can affect any location. Skin disorders facilitate infection. Among sexually active adults, the most frequent route of transmission is sexual contact and it is considered an STI when lesions appear in the genito-anal area. However, in children, lesions in this area are most often secondary to autoinoculation as long as there are lesions in other locations.

The incubation period of MC is unclear, but can vary between 2 and 6 weeks.

The use of barrier methods does not protect sexual partners from infection although it may reduce the risk of transmission.

Clinical picture:
MC causes a localised infection affecting the outermost layer of the skin and presents as superficial lesions in the form of small, non-pigmented, umbilicated, 3-5 mm papules that drain a creamy whitish material when squeezed. They are usually asymptomatic.[117]

Giant, extensive and persistent forms of MC have been described in immunosuppressed patients.[117]

Multiple episodes in the same patient should be considered reinfections, not reactivations.

Diagnosis:
The diagnosis of MC is clinical in the vast majority of cases.
The virus cannot be cultured in the laboratory and serology is not routinely used. In doubtful cases, a biopsy can be performed.

Differential diagnosis includes skin lesions due to cryptococcosis and histoplasmosis in immunocompromised patients. In immunocompetent patients, lesions caused by human papillomavirus such as warts or condylomas or tumour should be considered. Histological examination is required in these cases.

Treatment indications. [118]

- Sexually active people: to reduce the transmission of infection to their sexual contacts.
- Immunosuppressed patients: to prevent the spread of lesions and possible local complications.

Treatment:
The first-line therapies in the treatment of MC are cryotherapy, imiquimod and podophyllotoxin.[119]Curettage of lesions is a widespread option although it is not recommended where such lesions affect the genital area.

Some of these treatments may cause minor pain or discomfort and even small scars or permanent pigment changes.

Multiple chemicals in general with irritant potential have been used with varying responses to treat MC lesions and are not advised in the genital or facial area.

3.5.2.2. Mpox:

Definition:

Mpox (formerly monkeypox) is caused by an *Orthopoxvirus* belonging of the same genus as the *Variola* virus (responsible for smallpox) and the *Vaccinia* virus (used in the smallpox vaccine). With the eradication of smallpox, mpox became the most important and pathogenic *Orthopoxvirus* in humans.[120]

Epidemiology:

It is a zoonotic disease caused by Mpox virus that is endemic in Central (clade 1) and West (clade 2) Africa and where a significant increase in the number of cases has been observed over the last two decades.[120]

Mpox has emerged as an imported and re-emerging disease in Europe and America with a large outbreak with community transmission in 2022 (clade 2).[120,121]

Transmission:

Person-to-person transmission can occur: (i) direct contact with lesions, scabs, or body fluids; (ii) fomites; (iii) respiratory secretions (microdroplets); or (iv) vertical transmission.[120,121]

During the outbreak in non-endemic countries that began in May 2022, the sexual transmission route has been of major epidemiological importance.[122]

The incubation period is usually 5 to 13 days.

Clinical manifestations

Patients with contact/sexual transmission of Mpox may present with prodromal systemic symptoms including fever, malaise and myalgias followed by a characteristic rash starting at the site of virus inoculation (usually in the genitoanal, pharyngeal or perioral area). Lesions at the inoculation site appear as whitish papules (pseudopustules, without fluid content) with a tendency to central necrosis and subsequent ulceration. In addition, distant lesions (trunk, extremities, etc.) in the form of papules-vesicles-pustules, secondary to the spread of the virus, may appear.[123,124] The disease is usually self-limiting (clade 2), but may be complicated by mucositis (proctitis, tonsillitis, genital oedema), bacterial superinfection, ocular involvement and/or other complications (e.g. central nervous system involvement, etc.). Complications are more frequent in immunosuppressed individuals.[125]

Mortality can be up to 10% with clade 1 and less than 0.2% with clade 2. Mortality of up to 15% has been reported in HIV-infected patients with poor immune control (<200 CD4 T cells/µL). The main causes of mortality are bacterial sepsis and encephalomyelitis.[121]

Diagnosis:
The diagnosis of Mpox should be suspected in patients with compatible skin lesions and epidemiological risk factors for infection. Confirmation is done by PCR detection of Mpox DNA from a clinical specimen. Anti-Orthopoxvirus IgM antibodies are elevated 4-56 days after debut.

Treatment:
In immunocompetent persons with mild disease, treatment should be symptomatic. In patients with or at risk of severe disease or complications, tecovirimat should be considered.[125]

In patients with severe disease who are significantly immunocompromised: consider combination therapy with tecovirimat plus another agent (e.g., cidofovir or brincidofovir).[125]

Prevention:
Patients diagnosed with mpox should be isolated (contact and respiratory) until the condition is resolved. The smallpox vaccine is 85% cross-protective. It is recommended for people at risk due to epidemiological factors or occupational risk. High-risk post-exposure vaccination is recommended.[125,126]

3.5.2.3. Zika

Zika virus (ZIKV) is a *Flavivirus* transmitted mainly by the Aedes mosquitoes and distributed mainly in Latin America and Asia. It can also be transmitted sexually (most commonly from male to female) and vertically, from pregnant woman to fetus, which may cause microcephaly, brain tissue shrinkage and vision damage.[127]

The relationship between sexual transmission and the overall incidence of ZIKV is unknown. Most people experience mild symptoms (fever, myalgia, rash, etc.) or asymptomatic condition.

There is no specific treatment or vaccine at this time, although it is in development.

Prevention of transmission to the fetus consists of avoiding pregnancy (condom use or sexual abstinence) three months after male partners travel or experience symptoms of Zika infection, or two months for women. Prevention of Zika virus infection consists of avoiding mosquito bites in endemic areas (repellents and physical measures).

3.5.3 Ectoparásitos: (scabies, *pediculosis pubis*)

3.5.3.1 *Pediculosis pubis*

Definition:

Infestation by the parasite *Phthirus pubis.*

Epidemiology:

Infestation occurs worldwide and affects both sexes, especially adolescents and young adults. Epidemiological data are limited, incidence appears to be declining. In the UK, incidence fell from 1.82 to 0.07 % between 2003 and 2013. The tendency to remove pubic hair is associated with a decrease in incidence.[128]

Transmission:

The average lifespan of the female pubic louse is 3-4 weeks and she lays a maximum of three eggs/day, which attach to the pubic hair and hatch in 6-8 days. Transmission is by very close physical contact such as sexual contact, although it can also occur less frequently through clothing or bedding. Pubic lice do not transmit other infections, but are associated with the presence of other STIs.

Clinical picture:

Pediculosis pubis usually affects the pubic and perianal areas, but can also be found in the armpits or other hairy areas of the body (chest, eyelashes, etc.). The scalp is generally not affected.

Itching of the affected areas is the main symptom. In individuals with prolonged infestation, pale, bluish macules of 0.5 to 1 mm (cerulean macules) may develop as a result of injection of the louse's anticoagulant saliva during feeding. These lesions are usually found on the lower abdomen, proximal thighs or buttocks. Inguinal lymphadenopathy is present in some patients. Excoriations can become bacterially superinfected.

Diagnosis:

Diagnosis is clinical and is based on visualisation of parasites or 0.5 mm translucent nits (louse eggs).

Treatment indications: Presence of the parasite

Treatment: Topical pediculicides are the main treatments for lice pubis. In addition, nits must be removed mechanically (e.g. by nit combing). It is not necessary to shave the hair in the affected area, although it decreases the chance of recurrence.

Drugs of choice: [128]

- Topical permethrin 1% (neurotoxic effect on lice) For availability, safety and low cost or ivermectin 200µg/kg oral, two doses separated by one week**(IA-A**) or
- Topical benzyl benzoate (10-25%)**(IV-C**).

Alternative treatments:
Topical Malathion 0.5%, topical ivermectin 1% (well tolerated on pubic area) and sulphur formulas 6-33%. Lindane is no longer recommended because of its potential neurotoxicity.

More than one application may be necessary to eradicate the infestation. All clothes worn in the previous three days should be washed at high temperature.

Prevention:
Health education on symptoms of the disease and its mode of transmission. Control measures in the index case and its contacts. Screening for other STIs (present in 30% of cases). In children, consider sexual abuse. It is a notifiable disease.

3.5.3.2 Scabies

Definition:
Infestation by the *Sarcoptes scabiei* parasite (size approximately 0.4 x 0.3 mm, not visible to the naked eye). Females dig galleries in the skin where they lay two or three eggs a day.

Epidemiology:
It can affect people of any age, but is most common in children and young people in resource-poor countries. A systematic review estimated a worldwide prevalence of the disease ranging from 0.2 to 71%, highest in the Pacific region and Latin America. Although there are no data in Spain as it is not a notifiable disease, STI and dermatology centres report a significant increase in diagnosis.[128]
Transmission:
It is transmitted through direct and prolonged skin-to-skin contact, such as may occur between family members or sexual partners. Transmission via fomites is rare in classical scabies, and more likely in crusted scabies.

Clinical manifestations
The incubation period is 30 to 60 days in the first episode, much shorter if the patient has already been exposed to the parasite.

The typical lesion is described as an acarine furrow, 1 to 10 mm in length, which is almost pathognomonic of the disease, but may be difficult to identify as a result of excoriation from scratching or if there are few lesions. It is shaped like a fine, scaly line and sometimes has a point of entry at one

end which constitutes the "vesicle pearl". There are primary lesions (acarine furrow, vesicles and nodules) and secondary lesions (small urticarial papules, scratch lesions, excoriations, eczematous plaques and bacterial superinfection).

The most important manifestation of scabies is itching/pruritus, predominantly at night (egg-laying time). It is caused by host sensitisation (type IV hypersensitivity reaction). The areas most typically affected are: interdigital spaces, wrists, elbows, armpits, periumbilical area, pelvis, buttocks, genitals, knees and edges of the feet.

Crusted scabies (previously referred to as Norwegian scabies): It mainly affects patients with compromised cell-mediated immunity (e.g. AIDS, HTLV-1 infection, leprosy, lymphoma, adults with Down's syndrome) or altered sensitisation. The lesions are crusty plaques containing millions of parasites in a single individual, which is therefore highly contagious. Patients with crusted scabies may have eosinophilia in the blood test.

Diagnosis:
Diagnosis of scabies is mainly clinical (skin lesions, nocturnal itching and family or sexual transmission). Parasitosis is confirmed by microscopic examination of material obtained after scratching the furrows and demonstration of the mite, its eggs or droppings. Dermoscopy may also be used. Laboratory tests are not indicated (eosinophilia may be present).

Treatment:
Treatment involves eradication of the infestation, management of itching (antihistamines or if it persists after treatment, topical corticosteroids), management of complications (bacterial superinfection), treatment of close contacts and disinfestation of personal and bed linen to minimise transmission and recurrence of the infestation. Mites do not survive more than 3 to 5 days outside the human body.
Scabies can be treated with topical, oral or combined treatment.[128]

- Topic: Permethrin 5% (preferred), benzoyl benzoate 10-25%, precipitated sulphur 6-33%, and ivermectin 1%. (**Ib-A**).
- Oral: oral ivermectin 200 µg/kg in one dose and repeat in 7-14 days (**Ib-A**).

Permethrin topical is similar to oral Ivermectin and superior to all other topical treatments.
For Crusted scabies, use topical scabicide (permethrin 5% cream or benzyl benzoate 25% lotion) in combination, daily for 7 days and then 2-3 applications per week for 2 weeks and oral ivermectin 200 µg/kg (3-7 non-consecutive days: days 1,2,8 and in severe cases days 1, 2, 8, 9, 15 ± 22, 29).[128]

It is considered cured if the lesions and nocturnal itching disappear. If not cured, reassess carefully to rule out persistence or reinfestation (versus other pathology) and re-treat if confirmed. Combination or second-line treatments can be used.

In the paediatric population over 2 months of age, topical treatment with 5% permethrin is recommended (apply, leave on for 8-14 hours, then repeat after 7-14 days). For patients >15 kg, if there is treatment failure or outbreaks in institutions, oral ivermectin (200 µg/kg) can be administered.

Prevention:
Close contacts (cohabitants and sexual partners) in the last 8 weeks should be treated. Close contacts should treat simultaneously with the case. It is not a notifiable disease.

3.5.4 Non-sexually transmissible anogenital pathology

3.5.4.1 Very common non-pathological anogenital skin lesions:

Pearly penile papules (PPP):
These are benign millimetric lesions with a whitish pearly appearance found around the crown of the glans penis. Although asymptomatic and benign in nature, it is important to reassure the patient about the nature of the lesion.[129]

Vestibular papillomatosis (VP):
They are small, filiform, monomorphous, soft, non-pigmented, symmetrical, filiform projections located predominantly in the posterior vestibule. In some cases, itching, pain or burning may be associated with itching and may interfere with normal sexual life.[130] As with PPP, it is important to reassure the patient about the nature of the lesion and provide symptomatic treatment if necessary.

Plicomas:
These are thickened skin folds in the perianal area, unlike external haemorrhoids, they do not have dilated vascular tissue inside. Its aetiology is diverse, the most frequent being previous external haemorrhoids.

Fixed drug eruption (FDE):
This is a localised toxicoderma that frequently affects the genitalia in the form of one or more erythematous/violaceous plaques that may become eroded. Treatment consists of withdrawal of the causative drug and symptomatic measures. Multiple drugs have been linked to EFM, especially antibiotics, analgesics and anti-epileptics.[131] It may also occur after ingestion of food.

Lipschütz ulcers:
These are deep, painful, necrotic vulvar ulcers of non-infectious origin that most commonly affect young women and adolescents with no history of sexual contact. They are considered reactive lesions and have been linked to multiple systemic infections, especially Epstein-Barr virus and hepatitis B virus. They have also been linked to vaccines (SARS-Cov-2). In many cases no triggering infection is found. They resolve spontaneously within a few days. Management is symptomatic with oral analgesia and topical anaesthetics. Topical and oral corticosteroids may be helpful.

Lichen sclerosus (LS):
A chronic T-lymphocyte-mediated inflammatory dermatosis that frequently affects the anogenital area. Its aetiology is unknown and it may be associated with other autoimmune diseases. It is characterised by mucocutaneous lesions in thin, shiny plaques that may progress to erosion, atrophy and fibrosis. LS can therefore trigger deep structural changes in the genitalia or anus. In addition, the risk of malignancy is difficult to quantify as this pathology is under-diagnosed.

High potency topical corticosteroids are the first line of treatment that have been shown to achieve clinical remission and prevent progression to dysplasia / squamous cell carcinoma.[132]

Lichen simplex chronicus:
It presents in the form of thickened, xerotic and very pruritic skin plaques. Lesions respond to scratching or friction. They are more frequent in accessible areas and can be difficult to treat.

Treatments should be aimed at treating the underlying disease, reducing inflammation and breaking the itch-scratch cycle. High potency topical corticosteroids can be helpful, but the cause (usually scratching) must be eliminated for them to be effective.[133]

Common perianal pathology:

- An anal fissure is a painful lesion of the anal region that presents as a fine erosion or linear tear, which may extend from the pectineal line to the anal margin. It is most commonly located in the posterior raphe. These lesions are extremely painful and often significantly impair the patient's quality of life.
  Acute fissures are managed conservatively, while chronic fissures require pharmacological or surgical treatment.[134]

- A perianal fistula is a tubular tract that usually connects a perianal abscess to the perianal skin. Symptoms include discharge and sometimes pain. Although most fistulas are not associated with other conditions, they may be related to diseases such as Crohn's disease, hidradenitis suppurativa or infections. Diagnosis is made by physical examination and sometimes anoscopy, sigmoidoscopy or colonoscopy. Surgery is often required.

- Haemorrhoids are dilated vessels of the haemorrhoidal plexus in the anal canal. They can be external or internal. Symptoms are irritation and bleeding. Thrombosed haemorrhoids are often painful. Diagnosis is made by inspection or anoscopy. Treatment is symptomatic, hygienic-dietary or by elastic band ligation, injection sclerotherapy, infrared photocoagulation or, sometimes, surgery.[135]

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CHAPTER 4

SYPHILIS

4. Syphilis

KEY MESSAGES

1. **Increasing incidence of syphilis** in Spain and in the rest of Europe, especially in GBMSM.

2. The **diagnosis of syphilis** is based primarily on serology.

3. **Lumbar puncture** is recommended **in the presence of neurological symptoms** or serological failure.

4. **Treatment of early syphilis:** penicillin G benzathine 2.4 million IU intramuscular, single dose.

5. **Treatment of late latent, indeterminate, gummas and cardiovascular syphilis:** penicillin G benzathine 2.4 million IU intramuscular in 3 doses, administered weekly.

4.1 Introduction and epidemiology

Syphilis is an infectious disease caused by *Treponema pallidum* and is one of the most common STIs in Spain. The incidence of syphilis in our country has been increasing since 2014, reaching an incidence of 17.10 cases per 100,000 inhabitants in 2022 (8,141 reported cases).

- 89% of new cases occurred in men, most of them MSM, and 59.6% of cases were aged 25-44 years.[1]
- In Europe, the incidence in 2022 was 8.5 cases per 100,000 inhabitants, with MSM also being the most affected.[2]
- Syphilis is transmitted sexually, through maternal-fetal contact, through blood products in the absence of screening and through accidental contact in laboratories.
- The average incubation time after infection through sexual contact is approximately 3 weeks (10-90 days).

Classically, syphilis has been divided into phases or periods according to the estimated time since transmission. A distinction is made between early syphilis, which occurs within the first year of transmission, and late syphilis, which occurs after the first year (table 1).

Table 1: Clinical manifestations and treatment of early and late syphilis[3,8,13]

Syphilis	Name	Time since infection	Clinical manifestations	Treatment of choice	Alternative treatment
Early	Primary	10-90 days	Usually a single ulcer at the site of inoculation accompanied by painless lymphadenopathy.	PGB 2.4 M IU/IM (Single dose)	Doxycycline 100 mg/ PO/12H/14d
	Secondary	From 6 weeks after infection (2-24 weeks)	General symptoms, lymphadenopathies, rash, alopecia. Any organ can be affected		
	Early latent	During the first year after infection	Asymptomatic		
Late	Late latent	From the first year after infection	Asymptomatic	PGB 2.4 M IU/ IM/7 days for 3 weeks	Doxycycline 100 mg/ PO/12H/28d
	Tertiary		Gummas Cardiovascular syphilis Late neurosyphilis		

4.2 Early syphilis

The first clinical manifestation is known as primary syphilis, which consists of the formation of an indurated, painless ulcer at the site of inoculation (syphilitic chancre). It is typically described as a single lesion but can also be multiple (atypical and painful e.g. perianal) and present with painless locoregional adenopathy. Another site may be the oral cavity. This lesion resolves spontaneously after 1-6 weeks, even without specific treatment.

Secondary syphilis occurs in 25% of untreated infections and occurs 2-24 weeks after the onset of the chancre. The clinical picture reflects the lymphatic and blood-borne spread of the spirochete throughout the body. Systemic symptoms such as general malaise, anorexia, fever, myalgia, weight loss, generalised lymphadenopathy, non-pruritic macular, maculopapular, papular, or pustular rash are present. It usually starts on the trunk and at the root of the limbs and typically affects the palms and soles. In skinfolds, the lesions coalesce to form plaques called condylomata lata; mucous plaques are observed on the mucous membranes and areas of alopecia called moth-eaten alopecia appear on the scalp. ny organ, including the CNS, can be affected at this stage of the disease.

The term latent syphilis defines the existence of serological reactivity in the absence of symptoms. Early latent syphilis is latent syphilis that occurs within the first year of acquiring the infection. During the early latent phase, relapses in the form of luetic secondarism occur in up to 24% of cases, most frequently among PLHIV.[3]

4.3 Indeterminate and late syphilis

From the first year of infection, the late syphilis phase begins. During this phase, serological activity without symptoms is present, which we will refer to as late latent syphilis and indeterminate syphilis where the time since infection is unknown.

Approximately one third of untreated infected persons will develop a persistent, slowly progressive infection called tertiary or late syphilis. [3] All organs are affected and clinical manifestations occur 20 to 40 years after infection. Within tertiary syphilis we distinguish:

- Gummas syphilis, consisting of destructive granulomatous lesions affecting any organ, predominantly the skin or bones.
- Cardiovascular syphilis: this results in obliterating endarteritis of the *vasa vasorum* of the aorta with necrosis of the medial layer, aortitis and aneurysm formation, especially in the ascending aorta with valvular involvement.
- Late neurosyphilis: to be discussed in the next section.

4.4 Syphilis and CNS

Affection of the central nervous system begins early in the course of infection, when the treponema crosses the blood-brain barrier. This occurs in 25-60% of cases.

Neurosyphilis can be asymptomatic or symptomatic. Symptomatic neurosyphilis can be classified into early and late neurosyphilis.[4]

Asymptomatic neurosyphilis:
Spontaneous clearance will occur in a significant percentage (approximately 80%). Patients without such clearance will enter a phase of asymptomatic neurosyphilis, which may eventually progress to symptomatic neurosyphilis.

If, after a correct treatment, titres do not decrease at least twofold from the initial serological value within a given time (see follow-up section) and reinfection is ruled out, it is advisable to perform a lumbar puncture.

Early neurosyphilis:
Early neurosyphilis is characterised by meningeal and vascular affectation. It manifests as meningitis (headache, nausea, vomiting and stiff neck), ocular impairment (uveitis, retinitis, or neuritis), otosyphilis (hearing loss with or without tinnitus) or meningovascular affectation (stroke or coma secondary to ischaemia).
It usually occurs in the first years of infection and is accompanied by a clinical manifestation of secondarism.

Late or tertiary neurosyphilis:
Late neurosyphilis is characterised by parenchymal affectation. It may present as general paresis or tabes dorsalis. It usually occurs 15-20 years after infection.
General paresis begins with progressive dementia that starts with memory loss and personality changes, and progresses to severe dementia. Psychiatric disorders such as depression, mania or psychosis are less frequently described. On examination we could find dysarthria, hypotonia and altered reflexes.

Tabes dorsalis affects the posterior cords, manifesting as sensory ataxia and lacerating pain. Less frequently, paresthesia and gastric crises (epigastric pain, nausea and vomiting) occur. On examination, Argyll-Robertson pupil and absence of reflexes in lower limbs are characteristic.

4.5 Diagnosis of syphilis

Serology has been and is the main diagnostic method, but still has problems with the lack of specificity of non-treponemal tests and the poor correlation of treponemal tests with disease activity.[5]

Direct detection methods such as dark-field microscopy or direct immunofluorescence are now performed in very few laboratories and have given way to molecular techniques, which are rapidly becoming widespread.

a) Molecular techniques:

- PCR tests can directly detect *T. pallidum* DNA from lesion samples in primary (where it performs best) and secondary syphilis.
- They are designed as real-time multiplex PCR techniques within genital ulcer syndromic panels.
- They can also be used in CSF in cases of neurosyphilis or other sterile fluids such as vitreous humour or amniotic fluid.[6]
- These techniques have higher sensitivity than direct detection by microscopy and will depend on the type of sample and the stage of the disease.[7]

b) Serological diagnosis:

Reaginic or non-treponemal tests: Non-treponemal tests detect IgG or IgM to non-specific lipid antigens such as cardiolipin or lecithin released as a consequence of cell damage in both host and bacteria and are widely used for the assessment of infection status. The most common non-treponemal tests are RPR(Rapid Plasma Reagin) and VDRL (Venereal Disease Research Laboratory).

- They can be performed qualitatively or quantitatively allowing the follow-up of a treated patient and are based on macroscopic or microscopic flocculation methods respectively. These tests are generally sensitive, but not very specific, as there are entities in which false positives can appear, especially in pregnant women, autoimmune diseases, infectious mononucleosis or hepatitis, among others.
- They are usually positive 10-15 days after the onset of the primary chancre. The results of reaginic tests are expressed as antibody titres. Low titres (between 1/1 and 1/4) may be obtained in the earlier stages of primary syphilis or as a consequence of treated syphilis, but a low titre (1/2 or 1/4) may also be a false positive result if there is a negative treponemal test result. This may occur in approximately 2-5% of the population.[8]
- Titres above 1/8 are associated with active syphilis, except in cases of treatment control.
- They may lead to false negative results due to the prozone phenomenon.[9] This effect can be avoided by serial dilutions of the serum until the antibody titre (1/16) is sufficient to give a visible agglutination. This should be done if clinical suspicion of syphilis is high and the sample is negative, weakly positive or atypical (**B-I**).

- The usefulness of these techniques also lies in their ability to monitor response to treatment. A minimum four-fold decrease in antibody titre from the initial serum (two dilutions), using the same non-treponemal method, would indicate a response to the treatment given and is a criterion of good performance. In case of re-infection, these would be the tests indicated for diagnosis of syphilis due to persistent positive treponemal tests. An example could be from a patient serum with a 1/64 titre which after treatment drops to 1/8, this would indicate a significant variation with a 6-fold decrease in titre (3 dilutions) from the initial titre.
- Non-treponemal antibody titres may vary during the course of untreated disease.
- The good sensitivity of non-treponemal tests is not matched by their specificity, so a positive result needs to be confirmed by a more specific test, such as a treponemal test.
- After appropriate treatment, non-treponemal tests usually become negative, indicating that the infection has been cured. However, in some cases, these tests may remain positive at low titres and for life despite correct treatment without ever becoming negative. This is called the serofast phenomenon. This reaction can occur at different stages of syphilis, either in the primary, secondary or late stage of the disease. In general, this phenomenon is thought to be more common in the late stages of syphilis. The serofast phenomenon is more frequent in PLHIV. Proper follow-up is essential to ensure that this reaction is not related to an active infection or possible re-infection.

Treponemal tests: These methods detect IgM and IgG antibodies specific to *T. pallidum* antigens and are mainly used to confirm the presence of infection. The treponemal assays are qualitative. Several types of formats are commercially available for these tests.

There are manual assays such as FTA-ABS (Fluorescent Treponemal Antibody Absorption) or TPHA or TPPA(Treponema pallidum Hemagglutination). Other manual and automated versions include immunoblots, , immunoassays, enzyme immunoassays (EIA), and automated methods based on CLIA (Chemiluminescence). As with non-treponemal tests, they can also give false positive reactions.

POCT techniques in serology:
Immunochromatographic (ICT) POCT techniques are commercially available for the diagnosis of syphilis and are used in many countries for the prevention of congenital syphilis transmission, many in combination with HIV antibody detection. Most of them are based on the detection of treponemal antibodies, offering a qualitative value.[10]

A POCT device called DPP (Dual Path Platform) type ICT is available for the simultaneous detection of reaginic and treponemal antibodies in capillary blood, fingerstick blood and serum. This technology is based on the presence of bands in front of the different antibodies. In addition, it is equipped with a micro-reader capable of giving a quantitative value of the bands density. The various authors who have used this technique agree that it has a very good sensitivity and specificity for treponemal

tests but not for reaginic tests. Likewise, RPR titre values correlate well with titres higher than 1/8 with a sensitivity of 96.9% compared to titres equal to or lower than 1/4, which showed sensitivities of around 58.5-53.9%.[10]

Traditional versus reverse algorithm:
Currently, clinical microbiology laboratories with large sample volumes have started to use automated specific treponemal tests such as EIA or CLIA, using what is now known as the reverse algorithm.[11].

The reverse algorithm involves confirming this result with non-treponemal tests as it is able to identify patients with good response to treatment and/or cured syphilis as well as patients with untreated syphilis (**B-II**). However, it can also lead, in a high number of cases, to false positives (low positive predictive value), especially in low prevalence populations. It is therefore recommended to confirm this result with a different treponemal test than the one used for screening (EIA and TPHA) (**C-III**).

It is important to note that following a positive initial treponemal test, a non-treponemal test is required (Figure 1). There is a non-negligible number of patients in whom the first test comes back positive but the second test is negative. In these cases it is necessary to confirm this result with another classical treponemal test such as the TPHA, which may or may not verify our initial result. These conflicting results may occur in patients with past syphilis, treated or untreated, early syphilis, or in patients who have never had syphilis.

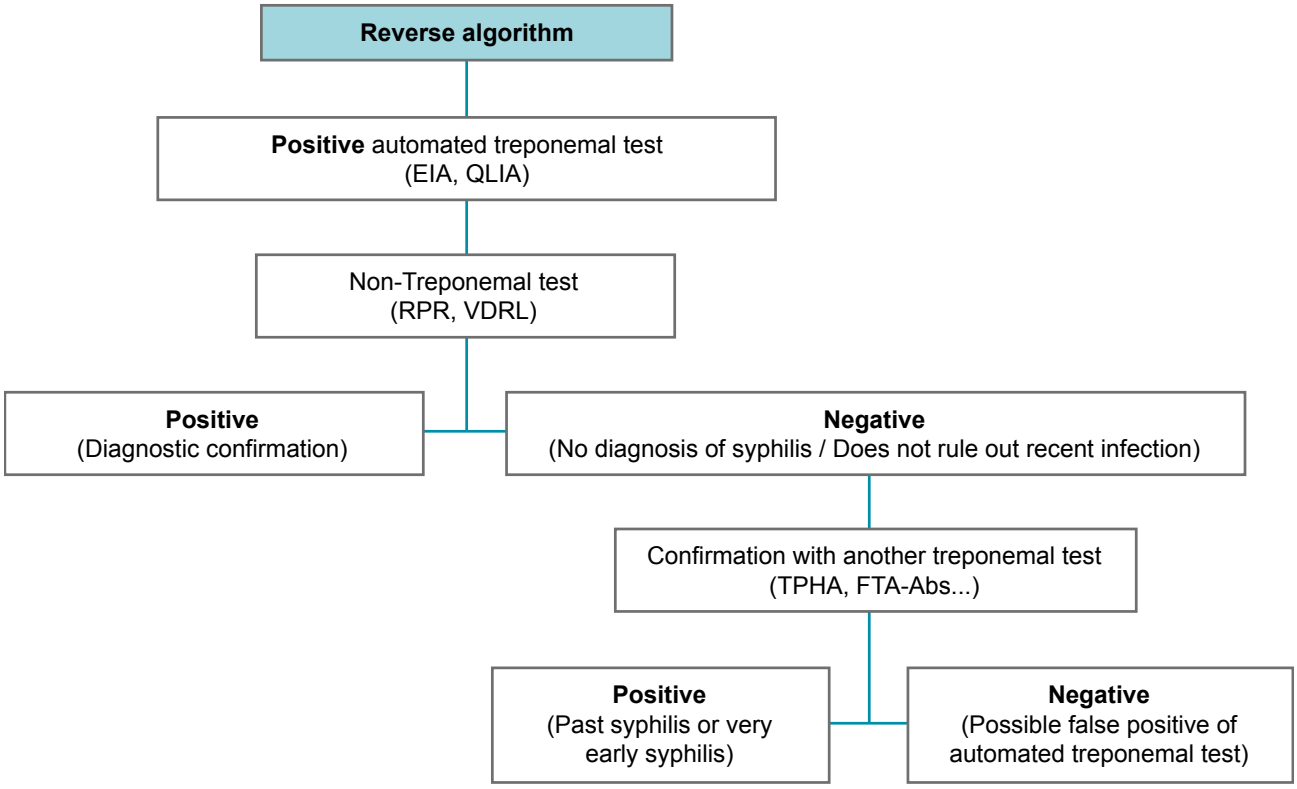
Diagnosis of neurosyphilis: [12]
In any patient with suspected neurosyphilis, a lumbar puncture should be performed in any of these cases:

- In the case of neurological symptoms. It is advisable to perform a funduscopy or CT scan prior to lumbar puncture, depending on availability.
- In the case of ophthalmic (uveitis) or auditory symptoms, LP is not necessary unless other neurological symptoms are present.[12]

Diagnosis of neurosyphilis is based on CSF abnormalities and non-treponemal tests. However, CSF biochemical alterations (>5 cells/mL and total protein values > 45 mg/mL) are only signs of inflammation and are not specific for neurosyphilis.

- Proteinorachia of >45 mg/ml together with cellularity (more than 5 leukocytes or 20 in PLHIV) would support the diagnosis.
- Non-treponemal tests (especially VDRL) are very specific but not very sensitive. A positive VDRL would indicate neurosyphilis (as long as the puncture was not traumatic).

Figure 1. Syphilis diagnostic algorithm[5,7,13]



4.6 Treatment

- Early syphilis: primary, secondary and early latent.[13-16 (12-14)]
  - 1st choice: penicillin G benzathine 2.4 million IU intramuscular as a single dose (**B-I**).
  - Alternative: doxycycline 100 mg PO every 12 hours for 14 days (**C-I**).

- Late latent syphilis, indeterminate, gummas and cardiovascular syphilis.[13-16 (12-14)]
  - Penicillin G benzathine 7.2 million IU intramuscular in three weekly doses (**C-I**).
  - Alternative: doxycycline 100 mg PO every 12 hours for 28 days (**C-III**).

In a recent meta-analysis, ceftriaxone 1g per day for 10 days could be an excellent alternative to penicillin for early syphilis.[15 (15-14)]

In patients treated with penicillin, especially in early syphilis, a so-called Jarisch-Herxheimer reaction can be triggered, which consists of the appearance 4-6 h after administration of a febrile syndrome with chills, headache, worsening of skin lesions, hypotension, tachycardia, hyperventilation, redness, myalgia, etc., which subsides approximately 24h later.[(16)]

Treatment for neurosyphilis:

The preferred treatment is penicillin. Treatment is the same in patients with and without HIV infection.

- 1st choice: penicillin G sodium 3-4 million IU I.V. every 4 hours or 18-24 million continuous infusion, both for 10-14 days
- Alternatives: Penicillin G procaine 2.4 million IU I.M. daily plus probenecid (500 mg/6 hours) for 10-14 days. Ceftriaxone (2 g I.V. per day for 10-14 days).[16]

In allergic patients, desensitisation is advised.[8]

4.7 Particular situations

Syphilis and HIV infection:

- Syphilis differs little in people infected with HIV, although atypical presentations, such as multiple chancres or malignant syphilis, may occur more frequently.
- Diagnostically, cases of syphilis patients with negative serology or delayed seroreactivity have been reported.
- In the diagnosis of neurosyphilis, as HIV infection itself can disrupt the blood-brain barrier, a cellularity greater than 20 mm^3 is used.
- Treatment regimens are the same as in HIV-negative subjects.
- The serological response is slower and the serofast phenomenon is more frequent.
- There is no difference in cure rates.[18]

Pregnancy:

Penicillin is the only treatment of choice, even in allergic patients, so if this is the case, desensitisation would be necessary.[19]

- In primary, secondary or early latent syphilis, the use of an additional therapeutic dose of penicillin benzathine (2.4 M IU I.M.) one week after the first dose of penicillin may be beneficial in these patients.
- Missed doses more than 9 days apart are not acceptable for pregnant people being treated for late latent syphilis. Should this happen, they will have to repeat their treatment.

Paediatric evaluation of the newborn of a mother with syphilis is advised [19].

Penicillin allergy:

In penicillin-allergic patients, the preferred treatment is doxycycline, which has been shown to be effective.[16]

- Early syphilis: doxycycline 100 mg PO every 12 hours for 14 days (**C-I**).
- Late syphilis: doxycycline 100 mg PO every 12 hours for 28 days (**C-II**).

Another alternative could be ceftriaxone, although there is a possibility of cross-reactivity with penicillin.[16] On the other hand, azithromycin is not recommended because of the high rate of macrolide resistance.[21]

Paediatric population:
These guidelines only address the diagnosis and treatment of sexually acquired syphilis, and specific guidelines should be consulted in the case of vertically transmitted syphilis or congenital infection.

Whenever primary or secondary syphilis is diagnosed in non-sexually active children and adolescents, the possibility of sexual abuse should be investigated.

In children, the basis of treatment does not vary, with penicillin being the preferred treatment. Dosage varies according to weight and, as in adults, according to the time of diagnosis of the infection:[22]

1. In cases of primary, secondary or early latent syphilis (infection in the year prior to diagnosis), penicillin G benzathine 50,000 units/kg IM in a single dose, up to a maximum dose of 2.4 million IU, should be administered.
2. When the diagnosis is established in late latent phase or of indeterminate duration, 50,000 IU/kg of penicillin G benzathine IM should be administered once a week for three consecutive weeks, not exceeding 2.4 million IU in each dose.
3. In severe cases or with central nervous system involvement, an expert in paediatric infectious diseases should be contacted.

4.8 Follow-up

All patients with syphilis should be tested for HIV and other STIs.[8]

After diagnosis, it is important to follow up clinically and serologically, to assess the response to treatment. The frequency and duration of this evaluation will depend on the diagnosis, whether or not the patient has HIV infection and the persistence of risk practices for reinfection.

Early syphilis:
The frequency of serological monitoring differs from guideline to guideline, although testing at 3, 6 and 12 months is recommended. In PLHIV, it is advisable to test at 3, 6, 9 and 12 months. In early syphilis, a decrease of two or more dilutions of non-treponemal tests at one year of follow-up is considered an adequate serological response.

Late syphilis:
In late syphilis, monitoring is extended to 24 months, with testing advised at 6, 12 and 24 months. In PLHIV, it is recommended at 6, 12, 18 and 24 months. In late syphilis, a decrease of two or more dilutions of non-treponemal tests at two years of follow-up is considered an adequate response.

Neurosyphilis:
More recent studies have shown a correlation between normalisation of RPR in peripheral blood and VDRL negativisation, so lumbar puncture could be avoided in cases of good clinical evolution and adequate serological response.[4] If no decrease in the RPR is observed, lumbar puncture is recommended at 6 and 12 months.[12]

Serological response patterns:
If the patient shows a decrease in the two dilutions, they are assumed to be cured, even if the RPR remains positive at low titres (serofast phenomenon).[5]

If the two-dilution decrease of non-treponemal tests is not observed with the stipulated time or a two-dilution increase is observed, it is advisable to perform a lumbar puncture to rule out asymptomatic neurosyphilis.

In the case that controls show an initial decrease of two dilutions with a subsequent increase of two or more dilutions of reaginic tests, a possible re-infection (symptoms, new contacts or untreated contacts) has to be assessed. If reinfection is suspected, treatment should be stage-dependent and contacts should be traced again. If reinfection is ruled out, a lumbar puncture should be performed to rule out asymptomatic neurosyphilis.[4]

4.9 Contact tracing

Contacts from the previous 3 months should be tested in the case of primary syphilis, contacts from the previous 6 months in the case of secondary syphilis, and contacts from the previous 12 months in the case of early latent syphilis. Patients with indeterminate latent syphilis with RPR ≥1/32 should be tested as in early latent syphilis.

All sexual contacts should be evaluated clinically and serologically if possible, and treated according to the following recommendations:[13]

- Sexual contacts in the 3 months prior to diagnosis of syphilis: treat as for early syphilis, even if serology is negative.
- Sexual contact more than 3 months ago: perform syphilis serology: If serology is negative, no treatment is required. If serology is positive, evaluate clinically and serologically. If serology is not available, it is advisable to treat as for early syphilis.
- Long-term sexual contacts of individuals with late latent syphilis should be evaluated clinically and serologically, and treated accordingly.

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CHAPTER 5

VIRAL HEPATITIS

Viral hepatitis

KEY MESSAGES

1. **Hepatitis A, B and C are liver infections caused by viruses.** All can behave as sexually transmitted infections.

2. In all persons with unprotected sex and risky behaviours, **active or past infection with HAV, HBV and HCV should be ruled out by serological testing.** As long as the risk situation persists, HCV screening should be repeated every 6-12 months.

3. **Vaccination** against both viruses **is indicated** for people with unprotected sexual relations and risky behaviours who **have had no previous exposure to HAV or HBV** .

4. **Chronic hepatitis B** is diagnosed by the presence of HBsAg for at least 6 months. People with chronic hepatitis B should be referred to a specialist for optimal care.

5. In **PrEP users with chronic hepatitis B**, tenofovir + FTC should always be used in a continuous pattern. The use of intermittent PrEP is contraindicated in these people because of the risk of HBV reactivation. A specialist should be consulted in advance if PrEP is to be discontinued.

6. **Hepatitis C** should be treated with DAAs as soon as it is diagnosed.

7. In **all persons with chronic hepatitis B, HDV co-infection should be ruled out** by testing for antibodies and, if positive, determining whether HDV replication is present by PCR.

5.1 Hepatitis A virus infection

Definition:

Hepatitis A virus (HAV) is a single-stranded RNA virus belonging to the Hepatovirus genus within the *Picornaviridae* family, for which humans are the main reservoir. There is only one serotype and six different genotypes. Only genotypes I-III infect humans, with IA being the most prevalent. It causes an acute infection of the liver, and does not cause chronic infection.[1]

Epidemiology:

HAV is highly prevalent in low- and middle-income countries. The virus is transmitted sporadically or epidemically from person to person through oral-faecal, water (rare in developed countries) and food routes. Faecal excretion begins one to two weeks before the onset of symptoms, and decreases with the onset of symptoms and with the presence of antibodies in the serum.[1] In Spain, the incidence of hepatitis A is very low, although outbreaks of sexual transmission occasionally occur, especially among men who have sex with men (MSM). For example, several phylogenetically related outbreaks of acute HAV infection were described in different European countries during 2016-2017. These outbreaks occurred in MSM and were associated with the use of HIV pre-exposure prophylaxis (PrEP) or having HIV infection. [2]

Clinical picture:

After an incubation period of 14-28 days, a clinical picture of malaise, anorexia, nausea, vomiting and jaundice may develop. However, it can often be asymptomatic, especially in children. The clinical picture can last up to two months, is usually not severe and resolves completely. However, 10-15% of those affected may have a prolonged illness lasting up to six months. In immunocompromised individuals, people with previous liver disease and older people, it can sometimes cause severe infection or fulminant hepatic failure. Hepatitis A never becomes chronic.[1]

Diagnosis:

Microbiological diagnosis of hepatitis A is made by determination of anti-HAV antibodies of the IgM and IgG types.[3] In some patients, these can be detected as early as 2-3 weeks after vaccination, so to avoid false positives they should be performed only in patients with symptoms or suspicion of acute HAV infection. In this case, IgM antibodies are detected 5-10 days before the onset of symptoms and may persist for about 4 months after infection.[3] IgG antibodies are detected near the onset of symptoms, preserve immunity for years, increase in prevalence with age and are indistinguishable from those generated by post-vaccination immunity.

Treatment:
There is no specific treatment for HAV. In symptomatic patients, treatment will be supportive.

Vaccination: (See also chapter 2.3. General prevention and control measures). All persons at risk of infection should be vaccinated. This involves people travelling to risky areas, health personnel and people with high-risk sexual behaviour. As discussed above, people on PrEP and people living with HIV (PLHIV) should be vaccinated against HAV. People with chronic liver disease should also be vaccinated because HAV can cause more severe disease in them (**A-I**).

In places with a low prevalence of HAV infection, such as Spain, pre-vaccination serology is not necessary, although if it is known and positive, it would prevent vaccination.

HAV vaccines are highly immunogenic and induce neutralising antibodies in more than 94% of subjects one month after the first dose and in almost 100% after the second dose.[4] In PLHIV, immunogenicity may be lower. This loss of immunogenicity is associated with lower CD4+ lymphocyte counts, with HIV viraemia >1,000 HIV RNA copies per ml at the time of vaccination and with male sex.[5]

Two inactivated HAV vaccines are currently marketed in Spain, Havrix (1,440 ELISA units for adults and 720 ELISA units for persons aged 1 to 18 years) and Vaqta (50 units for adults and 25 units for persons aged 1 to 17 years). Combined hepatitis A and B vaccines are also available. In adults, children and immunocompromised patients, HAV vaccination is given in two doses, with the second dose administered 6-12 months after the first.[4]

Post-exposure prophylaxis:
It should be administered to unvaccinated, previously uninfected persons who have had close contact (including sexual contact) with a person with hepatitis A.[4] In non-immunocompromised people between 1 and 50 years of age, initiation of vaccination will be sufficient. In individuals over 50 years of age, those with chronic liver disease or immunosuppression, it is also necessary to administer non-specific immunoglobulin at a dose of 0.02 ml/kg intramuscularly (I-B).

5.2 Hepatitis B virus infection

Definition:
Hepatitis B virus (HBV) is a small hepatotropic DNA virus of the *Hepadnaviridae* family that causes hepatitis B. It is transmitted by direct contact with infected body fluids. In Spain, the main routes of transmission are unprotected sexual contact and intravenous drug use. In highly endemic countries, perinatal infection is the most frequent route.

Epidemiology:

WHO estimates the global prevalence of HBV infection at 3.5%. Since the introduction of HBV vaccination into routine immunisation schedules, Spain is a low-prevalence country with figures around 0.5-1%.[6,7]

Clinical picture and natural history:

The incubation period from infection to the onset of symptoms ranges from 6 weeks to 6 months. Acute HBV infection is more than half of the times asymptomatic, although it can sometimes present as asthenia, abdominal pain, vomiting and jaundice. In 1% of icteric forms, the disease may progress to fulminant hepatitis. With regard to chronic HBV infection, the clinical spectrum ranges from the asymptomatic carrier to chronic hepatitis, cirrhosis and the development of hepatocellular carcinoma (HCC).

Fortunately, 95% of acute hepatitis B in immunocompetent adults resolve spontaneously and do not become chronic. Chronic hepatitis B is a dynamic process resulting from the interaction between HBV replication and the host immune response. There are 4 non-consecutive stages of active infection and one of functional cure which are defined by the presence or absence of HBeAg, virus DNA and ALT levels, and liver inflammation (Table 1) and should therefore be part of the initial evaluation of the patient with chronic hepatitis B (A-I). The characterisation of the stage of chronic infection will allow us to estimate the risk of fibrosis progression and development of HCC, as well as the indication for treatment:

1. **HBeAg-positive chronic infection stage:** characterised by minimal liver necroinflammation and slow or no progression to fibrosis. It is a highly contagious stage due to its high levels of HBV-DNA.
2. **HBeAg-positive chronic hepatitis or immune activity stage:** increased liver necroinflammatory activity and progression to fibrosis.
3. **HBeAg-negative chronic infection stage:** minimal or no liver necroinflammatory activity and little progression to fibrosis. Patients in this stage have a good long-term prognosis.[11] Loss of HBsAg with development of anti-HBs may occur spontaneously in 1-3% of cases annually, after several years with undetectable HBV-DNA.[12]
4. **HBeAg-negative chronic hepatitis B stage:** this is the most common stage in our setting and the one with the highest risk of progression to cirrhosis.
5. **Functional cure stage:** characterised by loss of HBsAg and minimal risk of progression to cirrhosis, decompensation and HCC and improved survival. Those who already have cirrhosis are still at risk of developing HCC and screening protocols should be maintained. Reactivation of HBV replication may occur in the context of immunosuppression.[13]

Table 1. Characteristics of the stages of chronic HBV infection [8-10]

	HBeAg POSITIVE		HBeAg NEGATIVE	
	Chronic infection	**Chronic hepatitis**	**Chronic infection**	**Chronic hepatitis**
Previous terminology	Immunotolerant	HBeAg positive immune activation	Inactive carrier	HBeAg- chronic hepatitis
Quantitative HBsAg	Very high	High	Low	Intermediate
HBV DNA	>10 million	20,000-10 million	<2,000 (or <20,000)	>2,000 (or >20,000)
ALT	Normal	High	Normal	High
Fibrosis	None/minimal	Inflammation ± fibrosis	None	Inflammation ± fibrosis

Diagnosis:

Initial serological screening of a patient for HBV infection includes determination of HBsAg and anti-HBc. Anti-HBs completes the serological status in anti-HBc-positive patients and helps us to determine the vaccination status in anti-HBc-negative individuals.[14]

HBsAg establishes the diagnosis of hepatitis B and its persistence for more than 6 months is diagnostic of chronic infection. Its quantified value reflects the amount and transcriptional activity of cccDNA in hepatocytes. HBc IgM is the best marker of acute hepatitis B, as it disappears within 3-6 months, whereas IgG persists for life.[14] Anti-HBs usually appear weeks or months after acute infection. It should be noted that 10% of patients who clear HBsAg do not develop anti-HBs.

If HBV infection is confirmed (anti-HBc), further testing with other markers (**A-I**) will be performed:

- HBeAg and anti-HBe: these help determine the stage of chronic HBV infection. The presence of HBeAg indicates high levels of replication and infectivity. Their expression may not necessarily correlate with virus DNA levels.
- HBV-DNA: its level indicates HBV replication. It is preferably determined by real-time PCR techniques.

The isolated anti-HBc pattern may represent occult hepatitis, although its prevalence and clinical significance varies in different studies. A recent meta-analysis estimates the prevalence of global occult hepatitis to be less than 1% [15] and may be higher in PLHIV, people co-infected with other hepatitis or on haemodialysis. In the presence of an isolated anti-HBc positive, HBV-DNA testing should be considered, especially in immunocompromised patients or those with evidence of liver involvement (**B-II**).

The liver status study will be completed with the following methods:

- **Abdominal ultrasound.** It can detect signs of liver cirrhosis, portal hypertension and rule out HCC (**A-I**).
- **Non-invasive methods of assessing liver fibrosis.** Transient elastography (Fibro-Scan) is the method of choice. Values >7.2 kPa indicate significant fibrosis (F2-F4) and values >12.4 kPa, high probability of cirrhosis (F4)[15] (**A-II**). In case of significant liver inflammation with elevated ALT values, elastography is not recommended as it overestimates fibrosis values. Other biomarker-based methods such as APRI and FIB-4 are not recommended in chronic hepatitis B because of their lack of diagnostic accuracy[16,17] (**B-II**).
- **Liver biopsy.** It is not necessary except in cases where the liver disease may be related to other associated pathologies and the relevance of each of them in the liver status is to be assessed (**A-II**).

Treatment:

Current treatment options are not able to eradicate the infection. Their main objective is to achieve sustained suppression of HBV-DNA in order to improve survival and quality of life by preventing the progression of the disease and the development of associated complications (**A-II**).

Treatment is not always indicated and is reserved for the following situations:[7]

1. Patients with chronic hepatitis B with elevated ALT levels, HBV-DNA > 2,000 IU/mL and/or with moderate necroinflammatory activity and/or fibrosis (**A-I**).
2. Patients with compensated liver cirrhosis if HBV-DNA is detectable, even if the ALT value is normal (**A-I**).
3. Patients with decompensated cirrhosis (**A-I**).
4. Patients with a family history of HCC or extrahepatic manifestations, even if they do not meet all criteria (**B-II**).
5. Patients co-infected with HIV (**A-I**).

In patients with chronic infection who do not require treatment, six-monthly follow-up is necessary in case there are changes in the markers that could affect the prognosis and therefore the patient's care (**A-II**).

There are 2 treatment options (nucleos(t)ide analogues pegylated interferon (PEG-INF), the choice of which will depend on host, viral and hepatic factors (**B-I**).

Nucleos(t)ide analogues: Entecavir, tenofovir disoproxil fumarate (TDF) and tenofovir alafenamide (TAF). They are drugs with a high barrier to resistance, high antiviral potency and low toxicity. Preferable in case of need for prolonged treatment. The initial duration of treatment is indefinite. HBV treatment is generally indefinite, although discontinuation can be considered if HBsAg loss is achieved (in patients without cirrhosis, without extrahepatic manifestations, without immunosuppressive treatment and provided that they are to be closely monitored) (**B-I**).

PEG-INF alpha-2: Drug with dual antiviral and immunostimulant action, with higher HBsAg and HBeAg negativisation rates than analogues, although side effects limit its use. Predictors of response are high baseline transaminases, low HBV-DNA, and genotypes A and B. It is indicated for a maximum duration of 48 weeks (**B-I**). In HBeAg-positive patients infected with genotypes A or D who, after 12 weeks of treatment, have a qHBsAg level >20,000 IU/mL and no decrease from baseline levels, treatment may be discontinued due to lack of efficacy (**B-I**). In HBeAg-negative patients infected with genotype D who, after 12 weeks of treatment, show no decrease in the qHBsAg level together with a <2 log10 decrease in HBV-DNA, in both cases from baseline, treatment may be discontinued due to lack of efficacy (**B-I**).

All patients undergoing treatment will be tested periodically for ALT and HBV-DNA. Patients on TDF treatment will be monitored for renal function and phosphate levels and those receiving PEG-INF will be monitored for haemogram and TSH (**A-I**).

Since most acute hepatitis B in immunocompetent adults do not become chronic, treatment (**A-II**) is not indicated except in cases of severe acute hepatitis, where treatment with nucleos(t)ide analogues should be initiated (**A-II**).

Paediatric population:
The indications for HBV treatment in the paediatric and adolescent population do not differ from those in adults, but the need to treat patients in these age ranges is exceptional and in the presence of chronic hepatitis B, patient follow-up by paediatric infectious disease experts is necessary. However, of the available drugs: entecavir and TDF are approved for children ≥2 years while TAF is approved for ≥12 years (and ≥35 kg) . PEG-INF is contraindicated in children under 1 year of age.

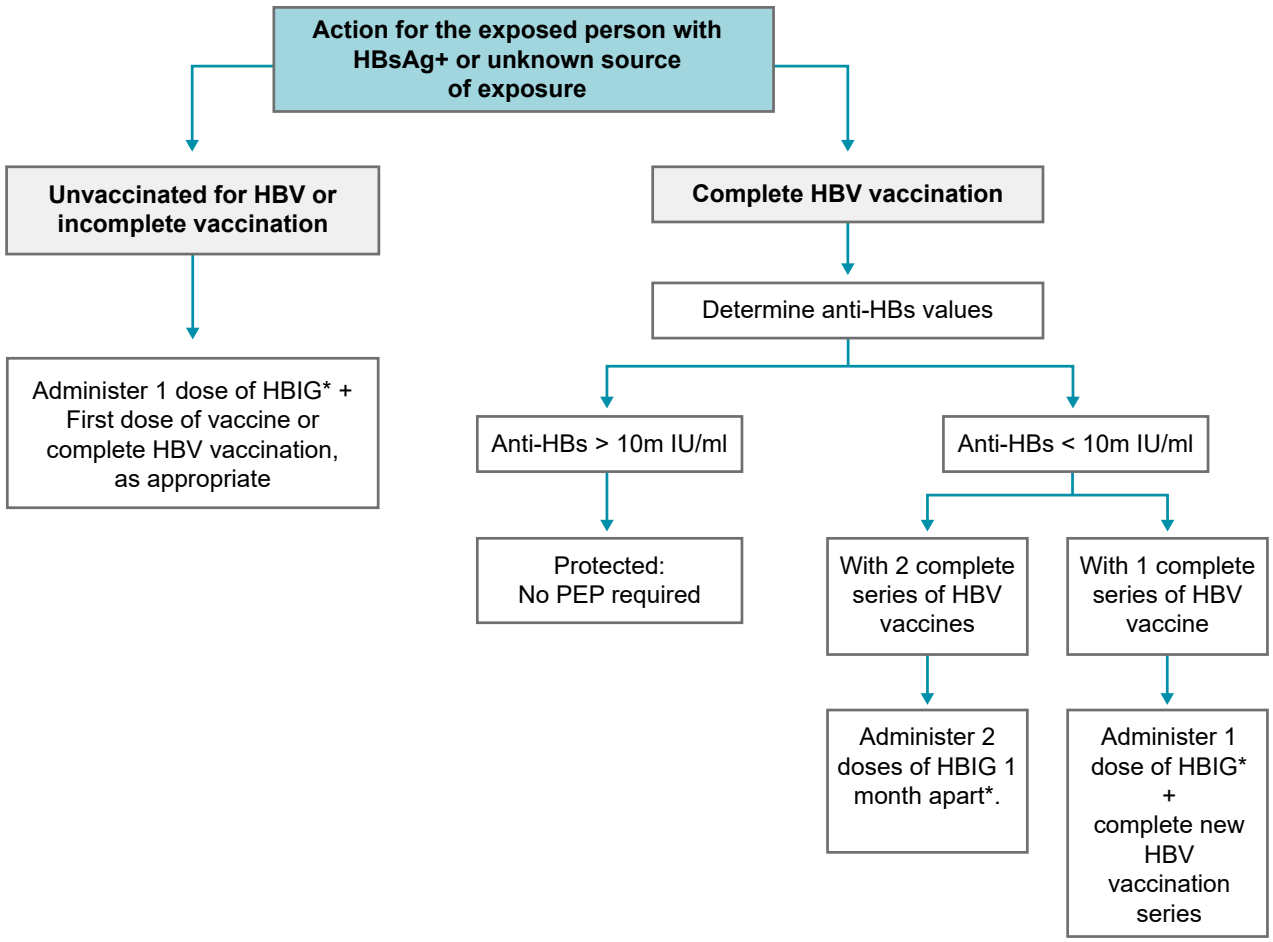
PrEP and PEP against HBV infection:
People at high risk of contracting sexually transmitted infections (STIs) and/or HIV, and therefore those on PrEP programmes, are also at high risk of hepatitis B, therefore screening and vaccination if appropriate are indicated (**A-II**). This issue is further developed in chapter 2.3. General prevention and control measures.

In people on PrEP programmes with chronic hepatitis B, there are a number of issues to consider. Firstly, the treatment of choice for HBV will be the TDF + emtricitabine (FTC) combination, as it matches that used for PrEP. It is not advisable to start treatment with entecavir because resistance to lamivudine or FTC may develop in case of HIV infection.

On the other hand, discontinuation of tenofovir therapy in people with chronic HBV infection may result in an increase in HBV replication, which may in turn be accompanied by severe clinical manifestations. Therefore, in people with chronic HBV infection receiving TDF/FTC as a PrEP strategy, intermittent PrEP should not be used and HBV reactivation should be closely monitored if PrEP is interrupted[18] (**A-II**).

For post-exposure prophylaxis, the recommended measures are set out in Figure 1.[19]

Figure 1. Post-exposure prophylaxis against HBV infection



*HBIG: Hepatitis B immune globulin; Dose 0.06 ml/kg (12-20 IU/kg) intramuscular. Administer preferably within 24 hours.

Contact tracing:
If a diagnosis of hepatitis B is confirmed, all first-degree relatives and sexual partners of the patient should be tested for HBV (HBsAg, anti-HBs and anti-HBc) and vaccinated if these markers are negative.[9]

5.3 Hepatitis C virus infection

Definition:
Hepatitis C virus (HCV), formerly known as "non-A, non-B hepatitis virus", is a single-stranded RNA virus, classified within the *Hepacivirus* genus, in the *Flaviviridae* family.[19] Seven genotypes have been identified; genotypes 1a and 1b are the most common in Spain.

Epidemiology:
According to the results of the second seroprevalence report in Spain, between 2017 and 2018, the prevalence of HCV antibodies in the general population aged 20-80 years in Spain was 0.85% while the prevalence of active infection was 0.22%.[20]

HCV is transmitted through direct contact with the blood of an infected individual. The sharing of infected injecting equipment among intravenous drug users (IDU), which was very relevant in the 80s and 90s, is still one of the main routes of infection in some Autonomous Communities despite its downward trend. Transmission has also been documented from sharing equipment for nasal drug use, especially if nasal or oral mucosa is damaged. Sexual transmission through semen or vaginal secretions in heterosexual intercourse is very inefficient. However, in recent years, we have seen an increase in the incidence of infections and re-infections associated with chemsex and slamsex, particularly in GBMSM, and it has come to be considered an STI in these settings.[21] As for other forms of transmission, vertical transmission of HCV has been estimated at 4-8%, increasing to 25% in HIV-infected mothers. Transmission related to health care, transfusion of blood or contaminated blood products was a frequent cause of infection until 1990 and has now been virtually eradicated. Tattooing and piercing in unsafe establishments and settings has also been associated with HCV transmission.[22]

Clinical picture:
The incubation period is between 5 and 24 weeks. Acute hepatitis C is usually mild and most of the time asymptomatic. It accounts for less than 15% of all cases of acute hepatitis, and when it occurs, it presents with very non-specific symptoms (malaise, nausea, anorexia), and less frequently in the form of a sudden onset of fever and abdominal discomfort. Elevated transaminases up to 10 times the upper normal limit may be found in cases of acute infection. Fulminant disease is extremely rare and should raise suspicion of co-infection with other viruses such as HIV.[19]

75% of cases of HCV infection progress to chronicity and up to 20% of chronically infected patients develop cirrhosis. Chronic hepatitis C is almost always asymptomatic until the typical complications of cirrhosis develop. When clinical manifestations are present in earlier stages, the most common symptom is asthenia, with jaundice being less common. Extrahepatic complications such as unexplained monoclonal gammopathy, mixed cryoglobulinaemia, cutaneous vasculitis and membranoproliferative glomerulonephritis may also occur, all related to immunocomplex production. Other non-immunocomplex extrahepatic manifestations include lichen planus, Sjögren's syndrome, diabetes mellitus, porphyria cutanea tarda and metabolic syndrome. Increased cardiovascular risk has been observed in patients with HCV chronic hepatitis.[19]

Diagnosis:

There are two main types of tests for the diagnosis of hepatitis C, anti-HCV testing and virological markers (virus RNA and core antigen). Both tests are performed on peripheral blood. While anti-HCV testing only indicates previous exposure or contact with the virus, virological markers indicate virus replication and infection activity. Determination of HCV RNA in serum or plasma by PCR is more sensitive than core antigen detection and allows identification of virus genotype and subtype, although viral genotyping is not indicated in all cases.[23] The techniques for determining anti-HCV and core antigen are EIA or its variant CMIA. A weak positive anti-HCV should be confirmed by Western Blot.

In people with risk factors for HCV infection (IDU, PLHIV, chemsex users, pre-1990 blood product recipients, incarcerated individuals, haemodialysis users, increased transaminases or repeat STIs), screening is recommended regardless of age (**A-II**). In populations at risk of reinfection such as IDU, PLHIV with risky sexual exposure (MSM with unprotected sex), PrEP users or people or those with frequent STIs, repeat testing is recommended every 6-12 months (**A-II**).[10]

Screening will be done by anti-HCV detection in the population with previous negative serology and by the presence of HCV RNA in those patients with previous positive serology (**A-II**). In situations with a high suspicion of acute infection and negative anti-HCV, HCV RNA testing may be considered.[23]

Treatment:

HCV infection is currently treated with direct-acting antivirals (DAAs), achieving cure rates of over 95%. Treatment is indicated in all patients with chronic HCV infection (**A-I**). Viraemia negativisation after 12 weeks (sustained viral response) is associated with normalisation of liver function tests and and regression of fibrosis in non-cirrhotic patients, as well as a decrease (not elimination) of the risk of clinical events related to chronic liver disease in cirrhotic patients.[24]

Pangenotypic regimens with sofosbuvir (SOF)/velpatasvir (VEL) (400 mg/100 mg) 1 tablet per day for 12 weeks or glecaprevir (GLE)/pibrentasvir (PIB) (100 mg/40 mg) 3 tablets per day for 8 weeks are currently the combinations of choice in non-cirrhotic AAD naïve patients.[24,25] Although other combinations offer similar efficacy, these offer the advantage of simplifying treatment by not requiring genotype for initiation (**A-I**). This indication is extended to naïve patients with compensated cirrhosis and non-3 genotype.

In naïve patients with compensated cirrhosis and genotype 3, there is more uncertainty about the optimal treatment and there are discrepancies between guidelines.[24,25] This is because there is a lower response with SOF/VEL in patients with the Y93H variation in the gene encoding the NS5A protein. Recently, guidelines on the management of liver disease in PLHIV by the Study Group for AIDS (GESIDA) and the Study Group for Viral Hepatitis (GEHEP) opted for simplifying treatment by indicating SOF/VEL for 12 weeks without the need for prior genotyping.[24,25] If the treatment of choice is GLE/PIB, it can be maintained for 8 weeks.

In patients with compensated cirrhosis who have previously received treatment with interferon and/or SOF, there are no trials assessing the efficacy of GLE/PIB administered for 8 weeks, but there are data on efficacies greater than 98% when treatment is extended to 12-16 weeks[24,25] (**A-I**).

Finally, in patients with decompensated cirrhosis, protease inhibitors such as GLE or Voxilaprevir (VOX) are contraindicated due to increased plasma levels and increased risk of decompensation. The SOF/VEL combination can be used, knowing that response rates are lower. The ASTRAL 4 study, which evaluated SOF/VEL efficacy in decompensated cirrhosis, showed that patients who received SOF/VEL plus ribavirin (RBV) for 12 weeks had higher sustained virologic response (SVR) rates than those who received only SOF/VEL for 12 weeks (94% and 83%, respectively). The division that studied the 24-week SOF/VEL regimen without RBV had an intermediate response (86%).[26] If treatment with RBV is decided, it can be started at 600 mg/day and increased according to tolerance.

Table 2 summarises the indicated treatment regimes.

Table 2. Indications for HCV treatment in patients with no previous experience of DAA combinations regardless of genotype[10]

HEPATIC DAMAGE	PREVIOUS TREATMENT	SOF/VEL	GLE/PIB
No cirrhosis	Naïve Previous experience*	12 weeks 12 weeks	8 weeks 8 weeks
Compensated cirrhosis	Naïve Previous experience*	12 weeks 12 weeks	8 weeks 12-16 weeks**
Decompensated cirrhosis	Naïve or previous experience	12 weeks + RBV 24 weeks	Contraindicated

*Previous experience with combinations including SOF + RBV, SOF + PEG-INF + RBV or PEG-INF + RBV + TPV or BOC.
**If the genotype is known, treatment can be extended to 16 weeks in patients with genotype 3. RBV doses are 1000 mg/day (<75 kg), 1200 mg/day (≥75 kg). It is possible to start with 600 mg and increase according to tolerance.

Special situations:

- Failure of DAA treatment (re-treatment): the SOF/VEL/VOX (400 mg/100 mg/100 mg) combination, one tablet per day for 12 weeks in patients with previous DAA failure, has achieved efficacies above 90% and is therefore considered the treatment of choice (**A-I**).[27] In patients with multiple failures, the study of HCV resistance to DAA may be useful in the choice of treatment, selecting at least two active drugs. These patients may benefit from extending treatment by 16-24 weeks and/or adding RBV. It is advisable to individualise each case and consult with experienced centres.
- Recently acquired hepatitis C: this is the name given to infection that has occurred within the last year.[21] Due to the high rate of infection and the low probability of spontaneous cure, early treatment with the same regimens and duration as in chronic disease is recommended (**A-II**).
- HIV co-infection: the same guidelines should be used as in HIV-negative patients (**A-I**). Potential interactions between antiretrovirals and direct-acting antivirals should be reviewed prior to initiating treatment.[10]

Paediatric population:

In children, the diagnosis of chronic hepatitis C is made when HCV+ RNA persists for more than three years. It is in these patients that treatment is indicated. Based on efficacy, safety and pharmacokinetic studies, the following combinations have recently been approved for use (FDA and EMA):

- Sofosbuvir/ledipasvir or Sofosbuvir/velpatasvir from the age of three.
- Glecaprevir/pibrentasvir for children over 12 years of age.

5.4 Hepatitis Delta virus infection

Definition:
Hepatitis D virus (HDV) is a defective RNA virus that requires the obligatory helper function of HBV for replication. Eight genotypes have been identified, with genotype 1 being the most widely distributed, predominantly in Europe and North America.[28]

While co-infection (simultaneous HBV and HDV infection) progresses to chronicity in only 2% of cases, superinfection (acute HDV infection in a person with chronic hepatitis B) results in chronic infection in more than 90% of cases.

The most common mechanisms of transmission are intravenous drug use, transfusion of blood products and percutaneous transmission. Sexual and perinatal transmission are less common.

Epidemiology:
The prevalence of HDV has changed over the past 25 years, reflecting the control of HBV infection due to the worldwide implementation of HBV vaccination programmes. It is estimated that around 4.5% of people with HBsAg have anti-HDV. Prevalence is higher in certain geographical areas such as Moldova, Mongolia and in Central and West Africa.[29]

Clinical picture:
There are two types of infection:

1. **Acute (3 to 7 weeks after initial infection):** fever, nausea, vomiting, jaundice. It is resolved within 6 months.
2. **Chronic:** more severe form of viral hepatitis due to more rapid progression to death associated with cirrhosis and HCC.

Diagnosis:
The diagnosis of HDV is determined by the presence of anti-HDV (IgM and IgG), which are found in all immunocompetent patients with the infection.[30] In all persons with hepatitis B, the presence of hepatitis delta should be ruled out.[14] Persons with anti-HDV should undergo molecular testing for detection or quantification of serum HDV RNA to determine if active infection is present (**A-II**). Viral load quantification is also useful in monitoring treatment response. HDV replication tends to suppress HBV replication, so HBV viral load is usually lower in co-infected patients.

Treatment:

In view of the progressive nature of HDV disease, treatment should be considered in all patients with chronic hepatitis D and active HDV replication (detectable HDV RNA), as high levels of HDV RNA have been shown to correlate with disease progression to cirrhosis and hepatocarcinoma. Only two drugs have been shown to be effective against HDV:

- **PEG-INF-α**: until May 2020, it was the only authorised treatment with only 30% of treated patients having a common SVR and long-term relapse due to the very high infectiveness of residual HDV. In addition, due to poor tolerability and poorer response, it is not recommended in HIV/HBV/HDV-infected patients (level of evidence **B-III**).[31]
- **Bulevirtide (blv)**: synthetic lipopeptide analogue to the preS1 domain of HBsAg, approved by the EMA in 2020.[32] It blocks HBV and HDV entry into hepatocytes by binding to and inactivating the sodium taurocholate co-transporting polypeptide (NTCP), a bile salt transporter that acts as an essential receptor for HBV/HDV entry. The available results show encouraging results: 45% of patients have undetectable HDV-RNA or a decrease of ≥ 2 log10 compared to 2% of those receiving placebo. It is administered by subcutaneous injection of 2 mg daily, with most side effects occurring locally. It is currently approved for use in patients with significant fibrosis and contraindicated if decompensated cirrhosis is present.

In all patients with chronic hepatitis D, the degree of liver fibrosis should be quantified by elastography or other non-invasive tests. In terms of management, HBV should be treated with TDF or TAF to suppress replication and to consider treatment with PEG-INF-α or BLV (level of evidence **B-I**).

If specific HDV treatment is chosen, the response will be monitored by monitoring HDV RNA as well as transaminases.

5.5 Hepatitis E virus infection

Definition:
Hepatitis E virus (HEV) is one of the most common causes of acute viral hepatitis worldwide; among the 8 different genotypes of HEV that have been identified, HEV-1, HEV-2, HEV-3 and HEV-4 can infect humans. The virus is transmitted via the faecal-oral route, mainly through contaminated water. Genotypes 3 to 8 are zoonotic and are transmitted by consumption of food derived from infected animals, mainly pork and game meat.[33]

Epidemiology:
There are an estimated 20 million cases of HEV infection each year, of which 3.3 million show symptoms of the disease.[3]

Clinical picture:
It generally causes acute hepatitis with an incubation period after exposure ranging from 2 to 10 weeks, with an average of 5 to 6 weeks. Signs and symptoms can last 1-6 weeks and are indistinguishable from other forms of hepatitis: fever, vomiting, abdominal pain, arthralgia, jaundice and hepatomegaly.

In rare cases, acute hepatitis E can be severe and lead to fulminant hepatitis (acute liver failure), which can be fatal. Pregnant women with hepatitis E, especially in the second and third trimester, are at increased risk of acute liver failure and death of themselves and their unborn child. In the third trimester, fatality rates of up to 20-25% have been reported.

In immunocompromised patients, acute infection may progress to chronic forms characterised by rapid progression of liver fibrosis.[35]

Diagnosis:
All patients with acute hepatitis should be screened for HEV. This screening should be based on the determination of anti-HEV and virus RNA (**A-II**). IgM anti-HEV are positive for a period of time (approximately 3-4 months) whereas IgG antibodies usually persist for years, so it is the detection of virus RNA in faeces and/or serum that indicates active infection.

Treatment:
To date, no specific drugs have been approved for the treatment of HEV infection. Fortunately, in the vast majority of cases, acute HEV infection can be cured spontaneously and does not require any specific treatment.

In patients with chronic hepatitis E, ribavirin (600 mg/12 hours) in short series of patients has been associated with SVR.[35] These data have not been correlated in acute hepatitis. Treatment with ribavirin is contraindicated in patients with gestational capacity due to its teratogenic potential.

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CHAPTER 6

HPV-RELATED PATHOLOGY

6 HPV-RELATED PATHOLOGY

KEY MESSAGES

1 **Human papillomavirus (HPV)** is implicated in the aetiopathogenesis of carcinoma of the cervix, anus, penis, vulva, vagina and oropharynx.

2 **Persistent infection with high-risk HPV,** especially HPV 16, as well as smoking, a higher number of sexual contacts or relations and immunosuppression are common risk factors for the development of anogenital and oropharyngeal squamous cell carcinoma.

3 **The diagnosis of anogenital warts (AGW) is clinical.** In case of doubts about the diagnosis, clinical atypia, treatment failure or immunosuppression, it is advisable to perform a biopsy to rule out dysplasia. Viral typing on the histological specimen is not routinely recommended.

4 With regard to the **treatment of AGW**, none has demonstrated superiority over the others, so the choice of treatment will take into account clinical variables, availability of treatment, as well as the preferences of the patient and the practitioner.

5 The **incidence of anal cancer (AC)** is increasing, especially in men who have sex with men (GBMSM) living with HIV, but also in all other people living with HIV (PLHIV), women with a history of other ano-genital neoplasias, solid-organ transplant recipients and non-LHIV MSM. Screening for its precursor lesion, HSIL, by cytology and high-resolution anoscopy is recommended in at-risk patients depending on available resources. Treatment of HSIL in PLHIV over 35 years of age has been shown to prevent the development of AC.

6 **Screening for cervical carcinoma (CC)** includes cytology at age 25-30, and HPV testing (with or without genotyping) and screening cytology from the age of 30. In PLHIV, screening starts at the age of 25 years with annual until the age of 30 years. Thereafter, triennial co-testing will be performed in women with CD4 > 200 cells/µL or with active antiretroviral therapy. Annual co-testing is recommended if CD4 < 200 cells/µL or not receiving antiretroviral therapy.

7 **Bivalent and nonavalent HPV vaccines** have shown efficacy in preventing premalignant lesions of the cervix, vulva, vagina and anus, as well as cervical and anal cancer. The nonavalent vaccine is also effective in preventing HPV 6 and 11-associated AGW.

6.1 Human papillomavirus. General

The human papillomavirus (HPV) belongs to the Papillomaviridae family, which consists of more than 100 types, of which at least 14 are considered to be of high oncogenic risk as they are causative agents of various types of neoplasms affecting both men and women.

Globally, HPV causes 1 in 20 cases of cancer in humans (1 in 10 in women). It is responsible for virtually all cervical cancers (CC)[1], about 60% of vaginal neoplasms, 40% of vulvar and penile cancers, 85% of anal cancers, and between 30% and 80% of oropharyngeal carcinomas.[2] Certainly, the relationship and involvement of HPV with cervical cancer is the best known.

HPV is transmitted mainly, but not exclusively, through sexual contact. It is estimated that approximately 50-80% of sexually active individuals come into contact with HPV during their lifetime.[1] The infection is most often acquired soon after the initiation of sexual activity (it is estimated that 39-55% of immunocompetent individuals, and up to 80% of immunosuppressed individuals, become infected within 24-36 months of initiating sexual intercourse), with peak incidence at 16-20 years of age, and can occur at any time in life.[3]

Risk factors associated with acquisition are related to sexual behaviour, including early sexual initiation and number of sexual partners. HPV vaccination before sexual intercourse is the most effective factor in reducing the risk of infection. In addition, male circumcision and consistent and correct condom use have also been shown to reduce the risk of transmission.[13]

HPV infection affects epithelial cells. Anatomical areas where there is a junction between two epithelia (squamocolumnar junction and metaplastic epithelium), such as in the cervix or anal canal, are particularly vulnerable areas. At this junction, basal cells with replicative capacity have an increased susceptibility to HPV infection. In contrast, other areas such as the vagina or vulva, characterised by poly-stratified squamous epithelium, present a more robust natural barrier, as the basal cells are less accessible to HPV. However, in these instances, there must be epithelial erosions or disruptions for the virus to gain access to the nucleated cells of the stratum basale.

Once it infects epithelial cells, it uses its replication and cell differentiation mechanism to generate new virions, thus spreading the infection.[4]

HPV infection is asymptomatic and in 80-85% of cases, it is self-limiting after months or years (spontaneous regression).[4] However, in 10-15% of cases HPV persists (years or decades).[24,5] Viral persistence is the necessary condition for the development of premalignant lesions capable of progression in the anogenital tract or in the head and neck area.[4]

Several factors have been described that increase the risk of HPV persistence, both viral (such as HPV 16 and, to a lesser extent, HPV 18 genotypes, integration of viral DNA into cellular DNA or high viral load) and host or environmental factors (immunosuppression, congenital or acquired, immunosuppression, smoking, prolonged use of oral contraceptives or multiparity). Persistence is associated with altered expression of oncogenes and tumour suppressor genes in epithelial cells, leading ultimately to oncogenic transformation. While these processes are well characterised in CC, they are less well known in the other HPV-associated tumors.[31,3,4]

6.2 Treatment of anogenital warts

6.2.1 Diagnostic aspects

Healthcare professionals familiarized with the clinical manifestations can diagnose anogenital warts (AGW) by physical examination **(D-I)**. Clinically, AGW are characterised by the presence of single or multiple, soft, smooth or papillomatous papules or plaques. It is important to rule out other sexually transmitted infections (STIs) and to carefully and thoroughly examine the entire anogenital area.[5] The diagnosis of AGW is usually made by visual inspection. In some cases of diagnostic uncertainty, a biopsy may be necessary, which is recommended for atypical lesions (e.g. pigmented, indurated, adherent to underlying tissue, bleeding or ulcerated) in immunocompromised patients (including those with HIV), uncertain diagnosis, lesions that do not respond to or worsen during standard treatment **(D-I)**.[46] Routine HPV PCR is not recommended for the diagnosis of AGW because the results do not have an impact on therapeutic management.[7] Biopsy can be done to remove or sample the lesion.[6] The application of acetic acid has a low positive predictive value for the diagnosis of external AGW[9], therefore, its use is not recommended[56] as a routine diagnostic tool.

6.2.2 General treatment principles

Treatment of AGW should be offered to all patients, as although they may resolve spontaneously, they can also spread to other areas and increase in size **(D-I).** Before prescribing a specific treatment, it is important to inform the patient extensively about:

I. Natural history of lesions (important to understand the outcome of treatment or the possibility of needing different treatments),
II. The purpose of the chosen treatment,
III. Treatment-related adverse effects, and
IV. The expected cure and recurrence rate.

There is no standard treatment proven to be superior, so the approach is personalised based on the number, size and location of warts, patient preferences, cost and adverse effects of treatment, as well as the practitioner's skills and the availability of therapeutic options.[9] A summary of the general treatment principles, considering the size, number and extent of the disease, is presented in the table below:[610]

Treatment overview

SIZE AND NUMBER OF WARTS	RECOMMENDED TREATMENTS
Single or multiple, small (<1 cm)	First-line therapies administered by the patient or physician. Physician-administered ablative therapies are preferred due to faster results compared to self-administered topical treatment, the effects of which are longer term. **1** Self-administered by the patient: - Imiquimod: 45-56% efficacy and 16% recurrence (**A-I**). - Sinecatechins: 50.8-64.9% efficacy and 10.3-11.8% recurrence (**A-I**). - Podophyllotoxin 15%: 74% efficacy and 11% recurrence (**A-I**). **2** Administered by the professional: - Cryotherapy: Once a week (up to 4 weeks), applied until freezing of the lesion (**B-II**). - Trichloroacetic acid: 39% efficacy (**A-I**). - Cidofovir: 63% efficacy in monotherapy; 100% efficacy and 27.3% recurrence combined with electrocautery. - Electrocautery in case of non-response to topical treatment of penile, anal or vulvar AGW (**A-I**). - Photodynamic therapy (PDT), second-line treatment for AGW of any location (**B-III**). - Proactive sequential therapy: sequential use of ablative treatments (cryotherapy), followed by the use of a topical immunomodulator (imiquimod, sinecatechins) (**C-III**).
Widespread disease (e.g. large plaques or exophytic nodules >2 cm)	Combination of topical agents with surgical excision, laser ablation or electrosurgery. Surgical excision: large lesions that do not respond to other treatments (**B-II**). CO2 laser is especially indicated in the case of large AGW or those located in anatomical areas that are difficult to access for other ablative techniques (**A-I**).

6.2.3 Topical treatments

Topical treatments are applied directly to the lesions and cause their destruction or disappearance by different mechanisms (cytotoxic effect by preventing cell proliferation or tissue destruction, or by activating local immunity). Depending on their mechanism of action, they can be classified into different groups:

6.2.3.1 Immunomodulators

Imiquimod:

Imiquimod is an immunomodulator that directly activates the innate cellular response and subsequently the adaptive response, and induces cellular apoptosis..[11] This treatment is indicated for anogenital warts of the external genitals, perineal, and perianal areas. **(A-I)**. Imiquimod 5% was approved by the FDA in the late 1990s as a treatment for external AGW, applied once daily 3 times a week until complete disappearance of the warts or for up to 16 weeks. In 2010, the FDA approved an Imiquimod 3.75% cream applied daily with cure rates similar to Imiquimod 5% but with fewer adverse effects, although it is not approved for this indication in Europe. The cream is applied before a night's rest and removed with soap and water upon waking after 8 hours. The most common side effects are local inflammatory reactions (erythema, itching, discomfort, stinging), although they are generally well tolerated. The clearance rate of lesions ranges from 45-56% and the recurrence rate is 16%.[12] It may compromise the integrity of latex in condoms and diaphragms. Sun exposure to the treated areas should be avoided.

Sinecatechins:

Sinecatechins are a partially purified fraction of the aqueous extract of green tea leaves from *Camellia sinensis*. This treatment is indicated for warts (or AGW) of the external genital, perineal, and perianal areas. **(A-I)**. Catechin ointment is available in 10% formulations in Spain. The mechanism of action on AGW is not fully understood, but appears to be related to the regulation of apoptosis-associated genes, which modulate/reduce factors involved in the proinflammatory response to HPV, and are anti-proliferative, anti-angiogenic and antiviral.[13] According to a meta-analysis[14], the effectiveness rate for AGW elimination is high (50.8%-64.9%), and the recurrence rate is low (between 10.3% and 11.8%). Regarding safety, this treatment is well tolerated, and adverse effects typically appear between the second and fourth week in more than 85% of individuals, these AE are usually mild and localized, such as erythema, edema, erosion, itching, and burning.. It is administered three times a day (morning, noon, and evening) for up to 16 weeks. It may compromise the integrity of latex in condoms and diaphragms.

6.2.3.2 Cytotoxins

Podophyllotoxin:

Podophyllotoxin inhibits the action of type II topoisomerase, an enzyme involved in DNA replication. Blocking the activity of type II topoisomerase prevents cell division and thus the multiplication of AGW cells. As the cells die, they are replaced by cells not infected with HPV.[15] Podophyllotoxin is

indicated for non voluminous or extensive AGW, especially if there is some degree of keratinisation **(A-I)**. Several doses and different formulations of gel, solution (preferably for use on the penis), and cream (primarily for vulva and anus) have been evaluated; is only applied in AGW twice a day for three consecutive days; if necessary, this can be repeated at weekly intervals for a maximum of 4 weeks. Due to the destructive effect of podophyllotoxin on cells, caution should be exercised when applying it to the affected area. Preparations containing podophyllotoxin are contraindicated in pregnancy; in case of open or bleeding lesions.[16] The most common adverse effects are local reactions at the application site, such as erythema, itching and burning sensations, and even skin erosion.[16]

Trichloroacetic acid:

Trichloroacetic acid (TCA) at a concentration of 80-90% is a caustic agent that destroys cellular proteins and causes cell death and is therefore indicated for the treatment of non voluminous or extensive AGW, especially if there is some degree of keratinisation **(A-I)**.[17] It should be administered by the practitioner (with a cotton swab until dry) to avoid damaging healthy skin. It is applied every one to two weeks and in most cases several cycles (8-10 weeks) are needed. The most common adverse effect is pain or burning during administration, although some people experience this for 5-10 minutes after application; ulceration may also occur, making this treatment unsuitable for voluminous AGW.[17]

Finally, it should be noted that the selection of a topical treatment for AGW among the available agents remains a challenge. There is hardly any good evidence comparing treatments for AGW. A network meta-analysis including data from 41 clinical trials with a total of 6,371 patients concludes that podophyllotoxin 0.5% solution was significantly more effective (74%) than imiquimod 5% cream (47%) (OR 1.94; IC95%: 1.02-3.71) for lesion clearance; however, it was associated with a higher overall rate of adverse events. It also concludes that 15% sinecatechin ointment was significantly less effective than 5% imiquimod cream (OR 0.21; IC95%: 0.12-0.34). The efficacy of trichloroacetic ointment was 39%, rising to 62% when combined with 25% podophyllotoxin.[718]

6.2.4 Ablative treatments

Cryotherapy:

Cryotherapy involves freezing the AGW with liquid nitrogen. Freezing causes permanent dermal and vascular damage, which triggers an immune response leading to necrosis and elimination of the destroyed cells. It is usually used in cases of multiple, small AGW, particularly those that develop on the shaft of the penis and on or near the vulva **(B-II).** It is usually done once a week for up to 4 weeks. It should be applied until complete freezing of the lesion and a "halo" of a few millimeters appears around the treated lesion. The main side effects include pain and pigmentary disturbances.[17]

Electrocautery:

Electrocautery is particularly effective for treating small AGW located on the penis, anus, or vulva, or for pedunculated lesions; however, it is not recommended as a standalone treatment but rather in combination with surgical excision in the area around the anus or vulva, or in cases of non-response to topical treatments (**A-I**). Electrocauterization may be painful, and the use of local or general anesthesia is typically required.[18]

Surgical excision:

Surgical excision of AGW is generally reserved for voluminous/large lesions that do not respond to other treatments (**B-II**), particularly when histopathological material is required for complete evaluation in cases where there is uncertainty regarding the benign or malignant nature of the lesion, or for small warts located in anatomically accessible areas. It is usually performed under local anaesthesia, and is particularly effective for condylomas and small warts. Surgical excision can cause scarring and changes in skin pigmentation.[17]

CO2 laser:

CO_2 laser therapy is the most commonly used laser modality and employs a concentrated beam of light energy. Absorption of the laser beam energy by tissue water results in vaporization through boiling of the intracellular and extracellular water. It can be used as a destructive or excisional treatment. Depending on the number and size of AGW, CO2 laser therapy can be performed under local or general anaesthesia. The main indications are large-volume AGW or those located in anatomical areas that are difficult to access with other ablative techniques, such as the anal canal or urethra **(A-I)**. Adverse effects include pain and irritation, as well as bleeding or scarring in the treated area. Treatment can be repeated if necessary. CO2 laser surgery is more expensive than other ablative techniques and its availability is limited.[17]

6.2.5 Other treatments

Cidofovir:

Cidofovir is a monophosphate nucleotide analogue which is a competitive inhibitor and an alternative substrate for viral DNA polymerases, disrupting chain elongation and thus viral replication.

It is indicated as a second-line treatment for AGW at any site **(C-III)**. For the treatment of skin disease, cidofovir is formulated as a 1% gel or cream and applied topically at night three times a week for up to 16 weeks, with an efficacy rate of 63%.[818] It has been used successfully in people living with HIV (PLHIV), together with electrocautery. This combination is an effective strategy to completely remove lesions and reduce the recurrence rate (to 27.3%).[917]

Photodynamic treatment with 5-aminolaevulinic acid:

Photodynamic therapy (PDT), based on light-induced, photosensitizer-mediated cytotoxicity—most commonly using 5-aminolevulinic acid (ALA), a precursor of protoporphyrin IX in the heme biosynthetic pathway—is a non-invasive therapeutic modality for the treatment of genital warts. PDT is of great interest due to its selective destruction of subclinical areas of virus excretion, activation of specific immune cells in the affected skin, alteration of local immunological parameters, and stimulation of the immune system. In addition, it offers the advantage of shortening the healing period and causing less disruption to local tissue integrity. It is indicated as a second-line treatment for AGW at any site **(B-III)**. One of its limitations has been the limited penetration depth of both the photosensitizer and the activating light, which makes it unsuitable for the treatment of large-volume warts.[19]

There is insufficient data demonstrating the superiority of one treatment over another; the choice depends on the characteristics of the lesion as well as on the preferences and available resources of both the patient and the clinician.

Proactive sequential treatment:

The term proactive sequential therapy has been defined as the sequential use of ablative treatments (cryotherapy, CO2 laser), until resolution of the lesions. Three to five days after re-epithelialisation, the immunomodulator (sinecatechins or imiquimod) is applied to the affected area for 12-16 weeks. The concept is considered to reflect standard clinical practice and is considered to be a strategy that allows rapid wart removal while reducing recurrences, which are particularly common in the first 6 months.[20] The effectiveness of this strategy should be confirmed in clinical studies **(C-III)**.

6.2.6 Treatment in special areas

The management of condylomas is also partially conditioned by the anatomical region involved—particularly in mucosal areas such as the vagina, cervix, anus, and urethra—and by the potential adverse effects or consequences associated with the available treatments.[21]

6.2.6.1 Vagina

Vaginal condylomas are typically multifocal and may present with variable extension. The most common treatments are CO2 laser, cryotherapy or TCA.[21] Immunomodulatory treatments do not include this indication in their prescribing information and may cause systemic adverse effects. Podophyllotoxin is contraindicated.

6.2.6.2 Cervix

Cervical condylomas require colposcopic examination for appropriate diagnosis and management. If they coexist with cervical premalignant lesions, excisional treatment with loop diathermy is performed. In cases of isolated condylomatous lesions, destructive treatments may be performed (CO_2 laser therapy, cryotherapy, or trichloroacetic acid).[21] Immunomodulatory treatments do not include this indication in their prescribing information. Podophyllotoxin is contraindicated.

6.2.6.3 Anus

Anal canal condylomas are usually managed with destructive procedures (CO_2 laser therapy, infrared coagulation, electrocautery, cryotherapy, or trichloroacetic acid). Although its use is off-label, imiquimod has been described in case series and clinical trials as either a standalone treatment or as an adjuvant to other procedures.[22]

6.2.6.4 Urethra

Urethral condylomas usually affect the distal part of the urethra and are treated with ablative treatments (often CO2 laser and cryotherapy) and less frequently with excisional treatments. It is important that treatments do not induce excessive scarring that could result in urethral stenosis.[21]

6.2.7 Treatment in special populations

6.2.7.1 Pregnancy

During pregnancy, condylomas may be observed throughout all areas of the genital tract. An expectant approach may be considered while awaiting potential regression; however, lesions relatively often increase substantially in number and/or size during gestation. Treatment aims to reduce viral load and exposure of the newborn during vaginal delivery. Large condylomas may rarely interfere with vaginal delivery; in such cases, an alternative mode of delivery (cesarean section) should be considered. However, if the condylomas do not physically obstruct the passage of the neonate, routine scheduling of a cesarean section is not indicated. The most common treatments during pregnancy include: destructive physical treatments (CO2 laser, cryotherapy), excisional treatments (electrosurgical excision), or TCA. A recent literature review considers cryotherapy to be the first-line therapeutic option in these cases, followed by

CO_2 laser therapy **(C-III)**.[1023] Sinecatechins are not authorised. Podophyllotoxin is embryotoxic and thus contraindicated.

6.2.7.2 Immunosuppression

AGW in patients with immune deficits tend to be multifocal, multicentric and more extensive, with poor response to treatment and a higher rate of persistence/ recurrence. Excisional treatments may be required for histological evaluation when the coexistence of premalignant lesions is suspected. Immunomodulatory treatments may be less effective **(C-III)**. Often several types of treatment (destructive, immunomodulatory, excisional) must be used in combination or sequentially.[24]

6.2.7.3 Childhood

At this age, spontaneous regression rates may reach up to 90% within two years, which supports an expectant management approach. A recent literature review shows that immunomodulatory agents (imiquimod topical 5% and 3.75% cream, sinecatechins 15% ointment) and cytotoxic agents (podophyllotoxin and cidofovir) are considered safe, effective and minimally aggressive in children.[24] It is important to note that AGW in childhood may be associated with sexual abuse, which should be taken into consideration especially in children over the age of 4 years.[1125]

6.2.8 Monitoring of anogenital warts

Up to 50% of women with AGW are co-infected with high-risk HPV, leading to synchronous or metachronous development of pre-malignant lesions in the anogenital tract.[21] Long-term follow-up studies of men and women with condylomas show an increased risk of other HPV-associated cancers (anogenital or head and neck). Therefore, women treated for condylomas should be screened correctly for cervical cancer. [21]

It is recommended that individuals diagnosed with AGW be followed up and screened for other STIs. Follow-up of patients treated for AGW allows verification of cure and diagnosis of persistence/ recurrence. Given the high recurrence rates, follow-up evaluations at 3, 6, and 12 months after treatment are recommended **(C-III).** Most recurrences occur in the first 6 months. In cases where persistence or recurrence is diagnosed, the same treatments may be repeated or different ones may be introduced depending on the response to the initial treatment.

6.3 Anal cancer

6.3.1 Epidemiology

Anal cancer (AC) is a rare neoplasm in the general population, although the last decade has seen an increase in both incidence and mortality from AC, especially in wealthy countries. The annual incidence of anal squamous cell carcinoma continues to increase globally by 2-6% per year, as does the mortality rate. 90% of squamous AC are caused by HPV, and the genotype most frequently implicated is HPV 16. Risk factors associated with anal cancer (AC) are primarily those related to HPV acquisition and persistence. These include a high number of sexual partners, receptive anal intercourse, men who have sex with men, individuals—particularly women—with a history of precancerous gynaecological lesions or HPV-related cancers, chronic immunosuppression (especially HIV infection, as people living with HIV have a 19-fold increased risk of developing AC compared with the general population, as well as recipients of kidney, liver, or heart transplants), and tobacco use.[26] A recently published meta-analysis found that the incidence rate in MSM PLHIV was 85 cases per 100,000 persons/year (IC95% = 82-89), in non-MSM male PLHIV it was 32 (IC95% = 30-35), and in female PLHIV it was 22 (IC95% = 19-24), with a strong variation by age (e.g. from 16.8 < 30 years to 107.5 ≥ 60 years for MSM PLHIV). The incidence of AC was much higher after diagnosis of vulvar cancer, 48 (IC95% = 38-61), than cervical cancer [9] (IC95% = 8-12) or vaginal cancer, 10 (IC95% = 3-30). [27]

6.3.2 Screening for anal cancer

We must differentiate between two concepts that imply completely different objectives and procedures. Firstly, screening for AC, aims to diagnose cancer at the earliest possible stage in order to improve the prognosis. It is performed by asking about anal symptoms (pain, bleeding, appearance of nodules/lumps), inspecting the perianal area and anal margin and performing a digital ano-rectal examination (DARE).[28] **(A-III)**

In contrast, screening for anal dysplasia aims to identify asymptomatic lesions of high-grade squamous intraepithelial lesion (HSIL), which is considered to be the precursor lesion of anal dysplasia. Most screening strategies for anal dysplasia rely on anal cytology, followed by high-resolution anoscopy (HRA) in cases of abnormal cytological findings, in order to identify and diagnose lesions, guide their management, and reduce the risk of progression to anal cancer.[29] **(B-III)** In recent years, screening strategies based on molecular tests such as HPV detection have been proposed (ref: IANS guidelines...). The main advantage of HPV testing is its high sensitivity and high NPV. However, there is currently no validated test for the virus. The remainder of this section will focus on screening for anal dysplasia. (DOI: 10.1002/ijc.34850).

6.3.2.1 Indications for screening

There is currently no consensus on who to screen. It should be considered in populations where the risk is significantly increased compared to the general population. This decision will be partly conditional on resources: if resources are scarce, we should focus on screening the most at-risk population where we have the most evidence of the benefits of screening, which includes PLHIV (over the age of 35, especially with low CD4 nadir). Within PLHIV prioritise GBMSM, followed by heterosexual men and women. **(B-II)** Other populations in which screening could be considered are women with genital HPV pathology (especially vulvar dysplasia/cancer), HIV-negative GBMSM, other causes of immunosuppression and people with anogenital warts[27,29] **(C-III)**, as the incidence of anal cancer is significantly higher than in the general population[27] (but ideally preceded by cost-effectiveness studies). The IANS consensus guidelines published in 2024[30] define two groups based on the incidence of anal cancer compared to the general population, depending on whether the incidence is more or less than ten times that of the general population. In group A (PLHIV MSM>35 years, all other PLHIV>45 years; HIV-negative GBMSM>45 years, HSIL/vulvar cancer from year of diagnosis, SOT>10 years after transplantation) screening is recommended. In group B (vaginal/cervical cancer/HSIL, anal warts, persistent HPV16 >1 year in cervix, other causes of immunosuppression) a shared decision is recommended from the age of 45 years.

6.3.2.2 Screening methods

6.3.2.2.1 Cytology

It is currently the most widely used screening method (**B-II**). It is performed by inserting a brush or swab dampened with water (lubricant cannot be used) through the anal margin into the rectum (about 6-7 cm), and slowly pulling it out in a rotating/circular motion with lateral pressure, to obtain a sample of cells from the entire circumference of the anal canal. Ideally, liquid-based cytology should be performed (less faecal contamination and possibility to perform complementary studies such as HPV screening). To be considered satisfactory, it must also contain rectal columnar cells, which ensure that the entire length of the anus has been covered, including the anal transition zone where the squamous epithelium of the anus and the rectal columnar epithelium meet. Unlike the cervix, the sample is taken blindly. It has a highly variable sensitivity depending on the risk groups analysed. It is generally considered to have suboptimal sensitivity, better in immunocompromised patients (PLHIV), males and in individuals with larger lesions. Sensitivity and specificity are around 85% and 43%, respectively.[31]

The cytological sample is classified, using the Bethesda system, into inadequate/unsatisfactory, normal, ASC-US (atypical squamous cells of undetermined significance), ASC-H (atypical squamous cells, HSIL cannot be excluded), LSIL (low grade squamous intraepithelial lesion or dysplasia), HSIL (high grade squamous intraepithelial lesion or dysplasia) and SCC (squamous cell carcinoma).[32]

Table 1: Incidence of anal cancer

POPULATION	AGE FOR SCREENING	INCIDENCE Cases/100,000 pers./year
Risk category A (incidence ≥ 10 times compared to the general population)		
GBMSM and TW with HIV	35	>70/100,000
Women with HIV	45	>25/100,000
Men who have sex with women with HIV	45	>40/100,000
GBMSM and transgender women without HIV	45	>18/100,000
History of vulvar HSIL or cancer	Within 1 year of diagnosis	>40/100,000
Solid organ transplant recipient	10 years after transplantation	>25/100,000
Risk category B (incidence up to 10 times compared to the general population)		
Cervical/vaginal cancer	Shared decision from the age of 45	9/100,000
Cervical/vaginal HSIL	Shared decision from the age of 45	8/100,000
Perianal warts (male or female)	Shared decision from the age of 45	Unknown
Persistent cervical HPV[16] (>1 year)	Shared decision from the age of 45	Unknown
Other immunosuppression (e.g. rheumatoid arthritis, lupus, Crohn's disease, ulcerative colitis, systemic steroid therapy)	Shared decision from the age of 45	6/100,000

Adapted from Stier EA, Clarke MA, et.al. International Anal Neoplasia Society's consensus guidelines for anal cancer screening. Int J Cancer. 2024 May 15;154(10):1694–1702. DOI: 10.1002/ijc.34850. PMID: 38297406

It is very important to stress that anal cytology should not be performed if there is no possibility of performing or referring for HRA. In this case, questioning of symptoms, inspection of the area and DARE should be completed **(A-III).**

6.3.2.2.2 HPV testing

HPV testing is not validated for use outside the cervix. It has a better sensitivity than cytology, around 92%.[1233] However, in populations at higher risk of anal dysplasia (such as PLHIV GBMSM), the prevalence of anal infection by different high-risk HPV genotypes (HR-HPV) is very high (70-80%, with approximately 30% of HPV 16), making it poorly discriminatory and of limited clinical utility.[27,34]

Some groups have considered its use for decision making, HRA is recommended if a normal cytology, ASC-US or LSIL is positive for HR-HPV or follow-up at one year or even two years if negative.[35] **(B-III)** In other risk groups where the prevalence of anal HPV is lower (e.g. women with HIV or women with genital HPV lesions), HPV testing may have a greater role as a screening tool.[34] **(C-III)**

The IANS guidelines published in 2024[1329] set out different scenarios on how to screen, either by cytology, HR-HPV testing or a combination of both, and the intervals for repeating these tests depending on the results, taking into account the different groups outlined above. However, most recommendations are based on expert opinion and there is no solid evidence to support them. The guideline does insist that if HRA cannot be performed, DARE should be done routinely in populations with a higher risk of anal cancer compared to the general population.

Although the 2024 IANS guidelines present the option of screening by HPV testing alone (with or without reflex cytology), this is not an efficient strategy in our setting.

SCREENING TEST	TRIAGE TEST	TEST RESULTS	MANAGEMENT	MODIFICATION FOR LOW HRA CAPACITY
Cytology	None	NILM	Repeat screening every 12 months	Repeat every 12-24 months
		ASC-US or +	Refer to HRA	ASC-US/LSIL - repeat after 12 months. HSIL and ASC-H - refer to HRA
	HR-HPV genotyping / ASC-US or +	ASC-US/ negative HR-HPV genotyping LSIL/negative HR-HPV	Repeat screening after 12 months Shared decision of physician and patient: referral to HRA or repeat screening	Repeat screening after 24 months Repeat screening after 12 months
		ASC-US or LSIL + positive HR-HPV	Referral to HRA	ASC-US/LSIL + HR-HPV (not 16 positive), repeat after 12 months. HPV 16 positive (irrespective of cytology, refer to HRA).
		ASC-H/HSIL (irrespective of genotyping)	Referral to HRA	Referral to HRA
Cytology + HR-HPV genotyping (co-testing)	None	NILM + negative HR-HPV	Repeat screening after 12-24 months	Repeat screening after 24 months
		ASC-US + negative HR-HPV	Repeat screening after 12 months	ASCUS + negative HR-HPV: repeat screening after 24 months
		NILM + positive HR-HPV (16 negative)	Shared decision of physician and patient: referral to HRA or repeat screening after 12 months	Repeat screening after 12 months
		LSIL+ negative HR-HPV	Shared decision of physician and patient: referral to HRA or repeat screening after 12 months	Repeat screening after 12-24 months
		ASC-US or LSIL + positive HR-HPV HSIL, ASC-H (irrespective of genotyping)	Refer to HRA	ASC-US/LSIL+ HR-HPV (not 16): repeat screening after 12 months. HSIL, ASC-H (irrespective of genotyping): refer to HRA

Low HRA capacity is defined as a greater than 6-month wait for referral to HRA due to an abnormal screening test. [30]

6.3.2.2.3 High-resolution anoscopy

HRA is the gold standard for anal dysplasia screening. It is performed using a colposcope for magnification and 3-5% acetic acid and Lugol staining to explore the entire squamous epithelium of the anus (including the anal transition zone) and the perianal area (area of skin including the 5 cm around the anal margin, in this area only acetic acid is used). The patient is usually in the left lateral decubitus position for this examination. HRA is intended to locate areas of suspected high-grade dysplasia (which may have increased acetic uptake, no lugol uptake, abnormal vascular patterns such as punctation or mosaicism).[31] The diagnosis of dysplasia should be made by histology through HRA-guided biopsies. The term AIN (anal intra-epithelial neoplasia) should no longer be used for biopsies and the classification is now LAST (lower anogenital squamous terminology), differentiating into LSIL (which includes what was previously classified as AIN-1) and HSIL (which includes AIN-2 and AIN-3).[32]

One of the limitations of the HRA is the learning curve. In fact, performance of HRA by an experienced professional is often the most limiting factor in the anal dysplasia screening programme.[28]

6.3.2.2.4 Biomarkers

p16 staining can be used to differentiate between low-grade and high-grade lesions in case of doubt.[32] The use of other biomarkers (p16/Ki67 dual staining, mRNA of E6/E7 viral oncogenes, viral and/or host gene methylation profiles, HPV integration), either in cytology or in biopsy, is experimental and therefore not recommended for routine use in clinical practice.[29,33] In the future, they may be useful tools to predict high-grade lesions that may revert to low-grade/normal or those that may progress to cancer, to make treatment and/or follow-up decisions, but at present there is a lack of evidence to support their application in clinical practice (**C-III**).

6.3.3 Treatment of high-grade anal dysplasia

Until the publication of the ANCHOR study[37], there was no evidence that treating HSIL lesions led to a reduction in anal cancer incidence, although some Spanish cohorts had suggested a clear benefit.[1438,39] In this study, there was the option to provide treatment (this approach is extrapolated from cervical disease; however, at the anal level, complete excision of the entire at-risk area is not feasible, unlike cervical conisation) or to monitor the patient with targeted biopsies performed every six months, based on a relatively low effectiveness, with a high rate of recurrence and a non-negligible percentage of side effects to the treatment. In addition, up to 20-30% of HSIL lesions resolved spontaneously without treatment.[37]

The ANCHOR study has shown that treating HSIL reduces the risk of anal cancer by 57% in men and women with HIV and therefore this treatment is recommended[1537] **(A-I)**. At present, these results cannot be extrapolated to other risk groups and more data will be needed before recommendations can be made.

Different topical (imiquimod, 5-fluorouracil, TCA 80-85%, cidofovir) or ablative (electrocoagulation, infrared coagulator, CO2 laser, argon plasma and radiofrequency) treatment options are available for HSIL (table 1). The choice will depend on the location and size of the lesion(s), but also on availability and experience, as there are few studies directly comparing the different options.[40] The most experienced treatment is electrocoagulation (in fact, 83% of ANCHOR patients were treated with this modality).[37] In general, ablative or TCA treatments are used for more localised lesions and topical treatments for larger or multiple lesions. They are usually performed on an outpatient basis, although depending on the size and the tolerance of the individual, they may exceptionally be performed in the OR.

Table 1: Topical treatment options for HSIL

	REGIME	EFFICACY	RECURRENCE	AE	COMMENTS
Topical					
Imiquimod 5%	3 times a week (night), up to 16 weeks	CR: 14-86% PR: 5-35%	39-71%	Pain, bleeding	Can be formulated as suppositories.
5-FU 5%	2 times a day, 5 days every 2 weeks, up to 16 weeks	CR: 9-86% PR: 0-27%	9-58%	Pain, bleeding	Less use in Europe, more use in the US.
TCA 85%	5 applic./session, 1-3 sessions 2-8 weeks apart	CR: 28-72% PR: 11-15%	8-15%	Pain, bleeding	Very well tolerated, no anaesthesia required.
Cidofovir cream 1-2%	2 g 3 times a week, 4-8 weeks	CR: 15-62% PR: 18-30%	13-25%	Pain, bleeding	High rate of AE.
Ablative					
ECG	1-3 sessions	CR: 22-78% PR: 7-26%	13-57%	Pain, bleeding	Maximum experience (83% ANCHOR patients). Risk of HPV inhalation.
IRC	1-3 sessions	CR: 3-71% PR: 6-69%	10-38%	Pain, bleeding	Slower than ECG. A specific instrument is needed. Risk of HPV inhalation.
CO2 laser	1-3 sessions	CR: NR PR: NR	--	Pain, bleeding	A specific instrument is needed. Risk of HPV inhalation.
PDT	Topical or IV photosensitising agent	CR: 20-40% PR: 27%	20%	Pain, bleeding, stenosis	Multi-zone disease. Little experience. Expensive
RF	Electrodes coagulate tissue at high temperature. 3 applications	CR: 58-100%	0-14%	Pain, bleeding (more than with other ablative treatments)	Circumferential or semi-circumferential treatment. Little experience. Expensive. Under sedation

Adapted from Brogden [40] DR et al. Int J Colorectal Dis. 2021; 36:213-22635. Treatment of anal HSIL. AE: adverse effects; CR: complete response; PR: partial response; 5-FU: 5-fluorouracil; TCA: trichloroacetic acid; ECG: electrocoagulation; IRC: infrared coagulator; PDT: photodynamic therapy; RF: radiofrequency. NR: not reported.

6.3.4 Other aspects

The age for starting and ending screening is not well defined, although most guidelines[1629,41] recommend starting at 35 years of age in PLHIV and do not consider continuing screening if repeated normal cytologies are obtained with negative HPV test results and there is no risk of reinfection (**C-III**).

An increasingly important aspect of the anal HSIL screening and treatment programme is the impact it can have on the quality of life and sexual health of those affected. There is a specific validated questionnaire (**A-HRSI**), also available in Spanish.

6.3.5 Anal cancer. Diagnostic and therapeutic approach

There are different types of tumours in the anus: squamous cell cancer (SCC), basaloid or cloacogenic carcinoma, adenocarcinomas and skin cancers (Bowen's disease, melanomas and perianal Paget's disease).[1727,42] Diagnosis is made by histology and often requires extensive biopsy or excision in the OR. Staging is performed according to TNM criteria through CT/NMR+/-PET-CT, and has an enormous impact on prognosis. Treatment consists of chemotherapy and radiotherapy. The exception would be localised tumours (<3 mm depth of membrane invasion and a maximum horizontal size of 7 mm), known as SISCCA, which could be treated by excision and well-differentiated (T1) and selected (T2) perianal carcinomas (N0) that do not involve the anal sphincter. It should be noted that the management of anal cancer is beyond the scope of this guideline. [1842]

6.4 Cervical cancer

Cervical cancer (CC) accounts for 10% of all cancers in women[1943] and is the fourth most common cancer in women worldwide, after breast, colon and lung cancer.[2040] In recent years, some countries have seen a significant decrease in the incidence of CC due to two interventions: 1) secondary prevention (implementation of screening programmes with cytology and HPV testing, detection of pre-malignant lesions and their treatment)[2140,41] and 2) primary prevention (HPV vaccination, especially if administered before the first sexual encounter).[2242]

Despite this, there are an estimated 529,000 new cases of CC annually, 85% of which occur in developing countries, with an estimated 275,000 deaths per year.[2343] Although there is great variability among countries, the global incidence is 13.1 per 100,000 inhabitants and the average age at diagnosis is 53 years.[2444]

6.4.1 General recommendations in immunocompetent and immunocompromised patients

CC screening starts with cytology at age 25, irrespective of the age of the first sexual encounter, vaccination status or other risk factors, and is continued with HPV testing from age 30-35. The incidence of CC under the age of 25 is extremely low and screening has not shown any benefit in reducing the incidence, so it is not indicated for women under the age of 25.

The most recent data indicate that in women living with HIV, the starting age for CC screening should not be changed: start at age 25[2547] with annual cytology until age 30 and then co-testing (cytology and HPV test) every three years in women with CD4 > 200 cl/µL or with active antiretroviral treatment. Annual co-testing is recommended if CD4 < 200 cl/µL or if not receiving antiretroviral treatment (CIII).

6.4.2 Algorithm for cervical cancer screening

The algorithm for CC screening includes cytology between the ages of 25 and 30 and HPV testing (with or without genotyping), and triage cytology from the age of 30 onwards.

The recommendations are summarised in Table 3 below.

Table 3. Algorithm for cervical cancer screening recommendations

Target population and screening strategy		Quality of evidence	Recommendation
Sexually active women between 25 and 65 years of age		Moderate	Highly recommended
Screening, irrespective of the test used, should ensure a population-based approach with coverage assessment mechanisms		Moderate	Highly recommended
Age	**Screening test**	**Quality of evidence**	**Recommendation**
Before the age of 25	No screening test	Moderate	Highly recommended
Between 25 and 30 years of age	Cervical cytology every 3 years	High	Highly recommended
Between 30 and 65 years of age	HPV test every 5 years (preferred option): - Determination of high-risk human papillomavirus (HR-HPV), regardless of HPV vaccination status. - If HR-HPV positive: appropriate triage for risk stratification of HPV lesions. - If high risk is ruled out, repeat HR-HPV after one year.	High	Highly recommended
	HPV test and cytology (co-test) every 5 years (acceptable option)	Low	Somewhat recommended
	Cytology every 3 years (acceptable option)	Moderate	Somewhat recommended
From 65 years of age	Finish screening (previous adequate and negative screening within the last 10 years and no CIN or CC within the last 20 years)	Moderate	Highly recommended
Hysterectomy (No previous CIN or CC)	No screening test	High	Highly recommended
History of lesion ≥ to HSIL/ CIN2	Screening at least 20 years	Moderate	Highly recommended
Immunocompromised individuals	Cytology from the age of 21	Low	Highly recommended
	Co-testing from the age of 30	Low	Highly recommended
Collection of screening samples			
Liquid-based cytology	Preferential		
Cytology, extension on slide	Acceptable		
Molecular tests, other means	Acceptable		

Table adapted from AEPCC-Guía: prevención secundaria del cáncer de cuello del útero, 2022 and Consensus Document on the modification of the Cervical Cancer Screening Programme [Documento de consenso sobre la modificación del Programa de Cribado de Cáncer de Cérvix]. Adaptation of the starting age for primary screening with HPV test and for screening in vaccinated cohorts. Ministry of Health, 2023.[47]

Following screening tests (HPV test with or without genotyping, and/or cytology) and taking into account factors that modify the risk of underlying lesion (previous screening result, previous colposcopy...), women whose result indicates a greater than 5% risk of high-grade intraepithelial lesion/cervical intraepithelial neoplasia grade 3 (HSIL/CIN3) should be referred for colposcopy (Figure 2).

For more information on the management of human papillomavirus in the cervix, please see: AEPCC-Guía: prevención secundaria del cáncer de cuello del útero, 2022 and the Consensus Document on the modification of the Cervical Cancer Screening Programme [Documento de consenso sobre la modificación del Programa de Cribado de Cáncer de Cérvix].

6.5 Other HPV-associated neoplasms

6.5.1 Intraepithelial neoplasia and penile cancer

Penile intraepithelial neoplasia (PIN) is considered the preneoplastic condition of penile epidermoid carcinoma, with risk factors overlapping those of penile epidermoid cancer (PEC). It is classified into undifferentiated PIN, caused by HPV, and differentiated PIN (caused by inflammatory skin diseases such as lichen sclerosus and lichen planus). HPV infection is associated in some countries with up to 34% of cases of penile cancer. Penile epidermoid carcinoma (PEC) is a rare cancer in high-income countries with an estimated prevalence of 0.1-1/100,000 men/year. However, in some regions of Africa, Asia and South America it accounts for up to 10% of malignant neoplasia in males.[50] Risk factors for PEC include lack of circumcision in infancy, phimosis, chronic inflammation, poor penile hygiene, smoking, immunosuppression and HPV infection. Treatment guidelines for PIN and PEC are based on data from small studies and case series, which recommend organ preservation procedures (glans resurfacing) whenever possible.[46] Advanced stages of the disease require a multidisciplinary approach. Research continues on the optimal sequence of treatments, and the selection of patients.[50]

6.5.2 Pre-invasive lesions of the vulva and vulvar cancer

The latest WHO classification (2022) classifies vulvar carcinomas and their precursor lesions based on their aetiopathogenesis, and differentiates between HPV-associated and HPV-independent carcinomas or lesions. HPV-independent lesions are called vulvar intraepithelial neoplasia (VIN). Pre-invasive intraepithelial lesions of the vulva associated with persistent HPV infection are called vulvar HSIL. The most common HPV genotypes with high oncogenic risk are HPV 16, 33 and 18.

The incidence of vulvar HSIL is 2.5-8/100,000 women per year with an increasing trend in recent years. The average age of the patients is 50 years (younger than in non-HPV-associated VIN). These patients share all the risk factors associated with persistent HPV infection such as the presence of other pre-malignant lesions in the anogenital tract, tobacco use, and immunosuppression, especially HIV infection.[51]

There are no secondary prevention programmes for these lesions, and diagnosis is based on the care of patients presenting with symptoms or as a finding on vulvar examination in asymptomatic patients. Proper diagnosis and treatment of these pre-invasive lesions (surgical, CO2 laser ablative, or imiquimod are the most frequent), is the only method to prevent the development of this neoplasm.

6.5.3 HPV-related head and neck cancer

Squamous cell carcinoma of the head and neck comprises a group of malignant neoplasms affecting the nasopharynx, paranasal sinuses, oral cavity, oropharynx, hypopharynx and larynx. The main classical risk factors are tobacco and alcohol. In recent decades, HPV has emerged as a new risk factor for oropharyngeal squamous cell carcinoma. HPV-dependent neoplasms are now considered a new tumour subtype that is biologically and clinically distinct from HPV-negative or HPV-independ-

ent neoplasms. In fact, the HPV status classifies two distinct entities and is the only clinically validated biomarker for survival in these cancers.[53]

The pre-malignant lesions of these tumours are so far unknown and there are doubts about the natural history of HPV infection at this site. The only possibility for potential prevention is to prevent HPV infection by administering prophylactic vaccines. As of 2020, the FDA added oropharyngeal and other head and neck cancers to the list of HPV vaccine indications based on their efficacy in preventing HPV-related anogenital diseases.[53]

6.6 Primary prevention of HPV lesions

At the time of publication of this Guide, two vaccines are available on the Spanish market (bivalent and nonavalent vaccines) that protect against infection with the most prevalent high-risk HPV types, responsible for 70-90% of pre-malignant and malignant lesions of the cervix, and a variable percentage in other anatomical sites (lesions of the vulva, vagina and anal canal). The nonavalent vaccine also protects against the HPV responsible for AGW.

The dosage of the marketed vaccines depends on the age at the time of initiating vaccination (see page 38, section 2.3.3.3). In Spain, the HPV vaccine is included and funded in the children's immunisation schedule at 12 years of age (**A-I**), as well as in certain groups such as individuals with WHIM syndrome, men who have sex with men up to 45 years of age, PLHIV up to 45 years of age, women treated for cervical HSIL with no age limit, sex workers up to 45 years of age and female transplant recipients (**C-III**). In addition to the above situations, where the vaccine is funded, the vaccine is recommended (even if not funded) for all individuals up to 26 years of age (**B-III**). Beyond the age of 26, scientific communities recommend a consensus on vaccination after assessing its benefit on an individual basis (**C-III**).[54]

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CHAPTER 7

SEXUAL ASSAULTS

7. Sexual Assaults

KEY MESSAGES

1. The repercussions of sexual violence include physical injury, STIs and pregnancy. The most prevalent microorganisms are *Chlamydia trachomatis*, *Neisseria gonorrhoeae* and *Trichomonas vaginalis*.

2. Care must be immediate and coordinated with legal and social services. If the time elapsed is less than 5 days, hospital care and judicial sampling are required; if longer, it will be dealt with in primary care with medical and psychological support.

3. The initial interview is key to obtain relevant details without forcing the victim. Medical and obstetric history and information about what happened should be collected, respecting the individual's pace and avoiding direct questions about the assault at the outset.

4. The examination should begin with the extragenital and paragenital areas, and then continue with the genital and anal regions. In addition, a prior explanation of each step to the victim shall always be ensured.

5. Sample collection should be performed whenever there has been significant physical contact. Testing for STIs is recommended regardless of the presence of symptoms.

6. Forensically relevant sample collection in cases of sexual violence must ensure the chain of custody and keep a detailed record of each step to avoid evidence invalidation.

7. Empirical treatment for gonorrhoea, chlamydia and trichomoniasis should be considered. In addition, HIV post-exposure prophylaxis (PEP) should always be assessed according to risk.

8. The victim's vaccination status should be checked, especially for hepatitis B and human papillomavirus (HPV). HPV vaccination will be recommended depending on age. Emergency contraception should also be offered when necessary.

9. Follow-up within one week is recommended, to confirm STI diagnoses and adjust treatments. Long-term counselling and follow-up HIV and syphilis serology at 6 weeks, 3 and 6 months are also crucial.

10. After initial care, the medical team should generate a detailed clinical report, including procedures and treatments performed. In addition, the forensic doctor will also write his own report for the court.

GLOSSARY

Sexual abuse:

This is a term that has fallen into disuse. Prior to the entry into force of Organic Law 10/2022 of 6 September, on the comprehensive guarantee of sexual freedom (Organic Law 10/2022 of 6 September, in the comprehensive guarantee of sexual freedom. Official State Gazette [BOE]: No. 215 of 7 September 2022 Reference: BOE-A-2022-14630), sexual abuse was defined in Articles 181 et seq. of Chapter II of Title VIII of Book II of the Penal Code. It was defined as the commission of acts that infringed on a person's sexual freedom and sexual indemnity without violence or intimidation and without consent. Non-consensual sexual abuse included acts committed against persons who were unconscious or mentally impaired, or when the perpetrator overrode the victim's will through the use of drugs, medications, or any other substance producing such effects. Sexual abuse was also deemed to exist when the victim's consent was obtained by taking advantage of a situation of physical or social superiority. Sexual aggression was defined in Chapter I of the aforementioned Title, Articles 178 to 180, as an attack on the sexual freedom of a person, through violence or intimidation. Since the entry into force of Organic Law 10/2022 there is no offence of sexual abuse in the Penal Code. Now, any act that infringes upon a person's sexual freedom without their consent is a crime of sexual assault.

Sexual assault:

Any act that infringes on the sexual freedom of a person without that person's consent is a crime of sexual assault. This has been the case since 7 October 2022, when Organic Law 10/2022 came into force, the fourth final provision of which amends Organic Law 10/1995, of 23 November, of the Penal Code by eliminating the distinction between sexual assault and sexual abuse. This definition is is reflected in the new wording of Article 178. This legislative change stems from the need for Spain to comply with the obligations assumed since it ratified the Istanbul Convention (United Nations Convention on the Elimination of All Forms of Discrimination against Women, the Council of Europe Convention on preventing and combating violence against women and domestic violence) in 2014. This change of perspective helps to avoid the risks of re-victimisation or secondary victimisation.

Substances of abuse:
Substances or drugs of abuse are those that by altering a person's reasoning or judgement can lead to health risks: from addictions to accidents caused by consumption or the acquisition of infectious diseases.

Rape:
The new wording of Article 179 of the Penal Code classifies rape as an aggravated form of sexual assault. The basic offence, according to paragraph 1 of this precept, involves carnal access by vaginal, anal or oral means, or the introduction of body parts or objects by one of the first two means.

Sexual violence:
According to Organic Law 10/2022 of 6 September on the comprehensive guarantee of sexual freedom, acts of a sexual nature that are not consensual or that condition the free development of sexual life whether in public or private spheres are considered sexual violence, including sexual aggression, sexual harassment and the exploitation of the prostitution of others, as well as all other crimes provided for in Title VIII of Book II of Organic Law 10/1995 of 23 November of the Penal Code, specifically aimed at protecting minors.

7.1 Sexual assaults and STIs

Epidemiology

The actual prevalence of sexual assaults is unknown, although data point to an increase in sexual violence (SV, a term that will be used generically throughout this chapter), which disproportionately affects women. According to a WHO analysis, in 161 countries between 2000 and 2018, one in three women have experienced physical and/or sexual violence.[1] US data suggest that approximately 26.8% of women (i.e. one in four) have been victims of rape, in contrast to 3.8% of men (one in 26). In addition, 47.6% of women have experienced non-consensual sexual contact, compared to 23.3% of men.[2]

In Spain, 8.9% of women aged 16 years or older report having been forced to have sex by a partner in their lifetime.[3] Reports of crimes against sexual freedom have increased recently. In Spain, 19,013 cases were recorded in 2022, 17,016 in 2021 and 15,319 in 2019, indicating an upward trend in these crimes except in 2020 due to the COVID-19[4]pandemic. In children, SV is one of the most frequent and severe forms of abuse. WHO estimates suggest that 1 in 5 females and 1 in 13 males suffer SV during childhood. In Spain, 5,449 notifications of SV in childhood were recorded in 2022, compared to 3,206 in 2021.[5]

The health impacts of SV include physical injuries, sexually transmitted infections (STIs) and unintended pregnancy. The likelihood of pregnancy after an assault is estimated at 5 per cent, with higher rates among adolescents. The incidence of STIs is unknown, and largely depends on local prevalence rates and type of contact. *Chlamydia trachomatis* (CT), *Neisseria gonorrhoeae* (NG) and *Trichomonas vaginalis* (TV) are the most prevalent microorganisms in SV victims. However, they are prevalent infections in sexually active populations, and often asymptomatic, so their detection in victims does not necessarily imply transmission related to the SV episode.[6,10]

7.2 Immediate attention to victims of violence against women

The care of victims of sexual violence requires effective coordination between the health care, judicial and social services sectors**(III-A**).[11-13] To prevent re-victimisation, protocols that promote collaboration between professionals and institutions are essential.

In most cases, the procedure begins with the notification to the corresponding Court of a possible case of SV.

The examination of the victim will be carried out in a coordinated manner, with a simultaneous clinical and forensic-medical assessment in a single procedure to confirm possible injuries and tthe collection of relevant samples. The victim shall be duly informed and his or her consent shall be obtained, as a breach of this requirement may lead to the test being invalidated. It is recommended that this forensic medical intervention be as early as possible and independent of the victim's complaint.

For further information, links to various guides of forensic interest are included:

- Good practice guidelines for forensic intervention with the victim of a crime facilitated by psychoactive substances: intervention in suspected chemical submission (2022); https://www.mjusticia.gob.es/es/ElMinisterio/OrganismosMinisterio/Documents/GBP%20actuaci%c3%b3n%20forense%20sumisi%c3%b3n%20qu%c3%admica%202022.pdf
- Performance in the care of child victims in the institutes of Forensic Medicine and Forensic Sciences (2017). https://www.mjusticia.gob.es/es/ElMinisterio/OrganismosMinisterio/Documents/1292430900758-Actuacion_en_la_Atencion_a_MENORES_VICTIMAS_en_los_IMLCFCMF_2018.PDF

Management will depend on the time elapsed since the episode. If it has occurred within the past 120 hours (five days), judicial sampling and medical attention are required, which implies a hospital referral, with the recommendation to avoid washing, changing of clothes and ingestion of food or liquids in cases of oral contact. When more than 120 hours have elapsed, it can be dealt with in primary care, where medical assistance and psychological support should be provided (NHS Common Protocol for Health Care Action against Sexual Violence 2023. https://www.sanidad.gob.es/organizacion/sns/planCalidadSNS/pdf/equidad/Protocolo_VSexual_12en2024.pdf).

The victim should be received in an appropriate manner in a discreet environment that ensures privacy and maximum physical and mental comfort, and encourages communication, confidentiality and a sense of safety and intimacy. The victim is encouraged to be accompanied by a trusted person at all times **(III-A**).

The action plan will include the following steps.[13-17]

1. Anamnesis and clinical examination:

The interview plays a key role in the assessment of victims of SV, as it provides the necessary information to guide the examination and sampling. In the first questions, the assault should not be directly addressed; instead, data will be collected on the identification of the victim, general medical history, pharmacological treatments, obstetric-gynaecological history in women (including age at menarche, date of last menstrual period, previous pregnancies). In addition, it is essential to record the history of consensual sexual relations, including the identification of partner(s) and the time of contact. The victim should be asked to relate what happened in his or her own words, interrupting as little as possible while describing the events. Information should be sought on the events (whether or not there was penetration, route, ejaculation, barrier measures), place, time, characteristics of the aggressor and approximate age; consumption of toxic substances, use of violence or restraint systems and post-assault behaviours (washing, eating, drinking, urinating, changing clothes or sexual relations after the event). If intoxicant use or exposure occurred, information should be collected on possible substances, routes of administration, time of exposure, and whether it was voluntary consumption.

The physical examination should begin with inspection of the extragenital and paragenital area, looking for lesions in areas of defence and resistance, support surfaces, and neck and breasts as typical areas where bruising may appear; finally, the genital area and anal region should be explored, preferably with the help of complementary magnification techniques such as colposcopy or staining of lesions. The condition of the hymen and anal sphincter shall be described. Each step must be carefully explained, taking the necessary time and always warning if physical contact is going to occur.

2. Sampling and testing for STI screening:

STI screening is not necessary in the investigation of all cases of SV **(III-A**).[10,18,19] The risk of infectious transmission depends on the type of contact and the prevalence in the general population. Since STIs can present asymptomatically, the absence of symptoms should not preclude testing. In general, it is considered that whenever there has been physical contact (genital/genital, genital/mucosal) under clothing, sample collection should be performed **(III-A**).

It should be noted that the victim's account may not be accurate, especially at first and in minors. Therefore, in children, adolescents and other vulnerable populations or when the victim was under the influence of substances of abuse at the time of the events, STI screening is recommended whenever risk practices are suspected.

Table 1 describes sampling for STI testing in cases of SV. During the joint clinical-forensic examination, a consensual sample collection is recommended in which samples are taken by location, following the order described in table 1b. Each case will be individually assessed, collecting microbiological samples according to the type of contact at the sites of penetration or attempted penetration, considering the need or not for extragenital sampling according to the account and circumstances of the facts.

Table 1. References Guidelines 2021, Seña, protoc VISEM [10,18,19]

SAMPLING FOR ANALYSIS IN SEXUAL VIOLENCE CASES[1,2,3]			
	ADULTS AND ADOLESCENTS (> 10 YEARS)	**CHILDREN PREPUBERTAL**	
TYPE OF SAMPLE	NO. OF SAMPLES		RECOMMENDED TESTS
Urine	Sterile container (5-10 ml) First part of urine	As in adolescents and adults	**NAAT**: NG, CT, TV, (+/- MG)
Conjunctive (with or without exudate)	1 medium Stuart or Amies swab 1 container swab suitable for NAAT	As in adolescents and adults	**CULTURE** NG **NAAT**: NG, CT
Oro-labial ulcer	1 container swab suitable for NAAT	As in adolescents and adults	**NAAT**: TP, HSV1 and 2
Pharyngeal exudate	1 medium Stuart or Amies swab 1 container swab suitable for NAAT	As in adolescents and adults	**CULTURE** NG **NAAT**: NG, CT, only PT if pharyngeal ulcer present
External ano-genital-external genital ulcer[4]	1 medium Stuart or Amies swab or swab container suitable for TAAN	As in adolescents and adults	**CULTURE** NG **NAAT**: +/- HSV 1 and 2, TP, CT
Cervical exudate[5]	1 medium Stuart or Amies swab 1 container swab suitable for NAAT	NOT RECOMMENDED	**CULTURE** NG **NAAT**: NG, CT, TV, +/-MG
Vaginal discharge[5]	1 medium Stuart or Amies swab 1 container swab suitable for NAAT	Only vaginal introitus and external vaginal area (labia majora and minora, clitoris, fourchette and mons venus). NOT RECOMMENDED in the internal vaginal area	**CULTURE** bacterial vaginosis,[6] NG **NAAT**: NG, CT, TV, (+/-MG)
Urethral discharge (male)	1 medium Stuart or Amies swab 1 container swab suitable for NAAT	NOT RECOMMENDED. Replace with URINE/HISOPO MEATO	**CULTURE** NG **NAAT**: NG, CT, TV, MG
Rectal exudate	1 medium fine Stuart or Amies swab 1 container swab suitable for NAAT Rectal speculum with proctoscope if proctitis is suspected	Blind swabbing: about 3 cm at the anal sphincter and rotate against the rectal walls for a few seconds. Avoid contact with faecal material	**CULTURE** NG **NAAT**: NG, CT, LGV, TV
Serum	Vacuum tube with serum separator gel 5 ml	Vacuum tube with serum separator gel 3-5 ml	Serology for syphilis, HIV, HBV, HCV
Other locations	*Pthirus pubis* on eyelashes/pubic hairs	As in adolescents and adults	Microscopic examination of the parasite

Notes:

(1) Microbiology laboratories may use specific swab systems and containers depending on the type of sample, the type of determination to be performed and the manufacturer's recommendations. Swabs should be chosen according to availability in health care facilities and microbiology laboratories, and Stuart or Amies media, with or without activated carbon, may be used.

(2) Due to the medical-legal implications, it is recommended that positive samples should be adequately stored in the laboratory in case further determinations are necessary.

(3) Samples are described in the most appropriate order of collection, not in order of priority.

(4) If exudate is observed, these swabs shall be collected before those for genetic identification.

(5) To be collected after swabs taken by the forensic scientist.

(6) Investigation for bacterial vaginosis is recommended especially if there is discharge, foul odour or itching.[10]

Table 1b. Sampling order for clinical and forensic analysis

ORDER OF SAMPLING AND TYPE OF ANALYSIS	
Type of samples	**Type of analysis**
Urine	Microbiological (5-10 ml) sterile vial
	Chemico-toxicological* (30-100 ml) sterile bottle
Conjunctive (if exudate) (ophthalmologist)	Microbiological
Oro-labial ulcer	Microbiological
Buccal swabs (dubitated/indubited sample)	Genetic
Pharyngeal swabs	Microbiological
Mouth washing	Genetic: 1 tube of washing liquid
Body surface swabs* (moistened)** (moistened)	Genetic
Swabs of external genitalia **** (moistened)	Genetic
External ano-genital-genital ulcer**	Microbiological
Cervical swabs	Genetic
	Microbiological
Vaginal swabs	Genetic
	Microbiological
Vaginal douching	Genetic: 1 tube of washing liquid
Urethral discharge (male)	Microbiological
Rectal swabs	Genetic moistened swabs (where recommended)
	Microbiological
Perianal swabs (moistened)	Genetic
Venous blood	Genetic (only if buccal penetration) 2 ml blood with anticoagulant EDTA
	Blood count, biochemistry and pregnancy test: 5 ml of blood without anticoagulant
	Microbiological (serum)
	Chemical-toxicological: 2 x 5 ml tubes of blood: (1 with sodium fluoride/potassium oxalate; 1 tube with EDTA)
Nails: clippings and swabs (moistened)	Genetic
Hairs	Toxicological: tuft from the occipital area close to scalp (7 mm diameter)
Other samples of forensic interest: Underwear and other clothing. Condoms, pantyliners, nappies, objects inserted into body cavities, chewing gum (in case of recent fellatio), etc.	Genetic

Notes:
*Chemical-toxicological analysis: Analysis consisting of the determination of substances of abuse, intoxicants or medication that may have influenced the victim's behaviour.
** Genetic analysis: In this context, genetic analysis or forensic genetic analysis is understood as the set of studies aimed at identifying possible biological traces from bodily fluids that may have been exchanged during sexual intercourse, and the analysis of genetic markers in these fluids to determine the person from whom they originate. All of these procedures are intended for the genetic identification of the alleged aggressor. Swabs for the collection of biological evidence for genetic analysis must be dry, with no medium of any kind.
***In women: labia, clitoris, hymen, fossa, fourchette. In men: penis and scrotum.
****In bruises, bites, fluid stains, etc. Two swabs from each area of interest.

Techniques for STI diagnosis should be highly specific. Samples collected prior to treatment should be retained in case further validation of the obtained result is required. In children, it is recommended that when a sample tests is positive by PCR, the result should be confirmed by repeating it on the original sample or by obtaining another sample.

7.3 Forensic sampling and forensic considerations

For microbiological samples from victims of GBV, it is essential to ensure the chain of custody (CoC), which guarantees the traceability of samples (evidence), at all stages of analysis (from the moment of collection to final storage or destruction). To fulfil this requirement, written and electronic documents (QC document) are needed stating where, when and by whom the samples were collected, as well as the log of movements and any incidents of the samples. Each professional involved at every step of the procedure must sign and record the time and date of the task or transaction performed. This includes forensic medicine professionals, gynaecologists, paediatricians, other clinical staff involved and laboratory staff responsible for the samples.[20] Once analysed, it must be noted whether the samples have been used up or if the surplus is stored (preferably refrigerated), where and for how long. Pathogen strains and nucleic acid extracts should also be frozen. There are no specific judicial recommendations on custody periods and it is recommended that each microbiology laboratory establishes a criterion on the length of this period, which should be documented according to laboratory policy..

The forensic doctor, depending on the account of the facts, the findings of the examination and the time elapsed, will decide on the samples to be collected for forensic analysis, also subject to the CoC. This point is outside the scope of this document and is not specified in this chapter.

Requests for complementary examinations for health care purposes shall be made on the usual hospital forms. It must be specified that a copy of the results of such tests shall be forwarded to the Forensic Clinic and to the relevant Court.

7.4 Treatment and Prophylaxis

Although the indication for PEP may be controversial due to the limited evidence, given the increasing prevalence of STIs and that follow-up may be complicated in the context of SV, empirical treatment for gonorrhoea, chlamydia and trichomoniasis could be considered. Always consider HIV prophylaxis according to risk 10**(A-III**) (table 2).

Table 2A. Treatment and prophylaxis according to population

SAMPLING FOR ANALYSIS IN SEXUAL VIOLENCE CASES[1,2,3]				
Population	**Sexually transmitted infection treatment and prophylaxis**	**HIV prophylaxis(1)**	**HBV prophylaxis**	**Contraception**
Non-pregnant persons	-Ceftriaxone 500 mg IM or IV single dose (SD) -Doxycycline 100 mg c/12h12 h PO 7 days. -Metronidazole or Tinidazole 2 g PO (SD)	Preferred guidelines: Raltegravir + tenofovir-D / emtricitabine (RAL + TDF/FTC). Every 12 h (AI) or daily **(AIII**) Dolutegravir + tenofovir-D / emtricitabine (DTG + TDF/FTC). Every 24 h, 2 tablets Doravirin / lamivudine / tenofovir-D or Doravirin + tenofovir-D / emtricitabine (DOR/3TC/TDF or DOR + TDF/FTC). Journal: 1 tablet (AI), 2 tablets **(AIII**). For more details and information on preferred and alternative guidelines, please refer to the SEIMC-GESIDA 2024 Consensus document on Post-Exposure Prophylaxis.	- Vaccinate if they are not already vaccinated - Assess gamma globulin See Chapter 5	**Yes < 72 hours** Levonorgestrel 1.5 mg PO (SD) **Yes > 72 hours** Ulipristal acetate 30 mg PO (SD)
Adolescents (both sexes)	-Ceftriaxone 500 mg IM or IV (SD) -Doxycycline 100 mg c/12h PO 7 days[2]	TDF/FTC or TAF/FTC + RAL bid or qd, or + DRV/b qd.or + DTG qd or TAF/FTC/BIC		Female adolescents: Yes < 72 hours Levonorgestrel 1.5 mg PO (SD) Yes > 72 hours: Ulipristal acetate 30 mg PO (SD)
Pregnant persons	-Ceftriaxone 500 mg IM or IV (SD) -Azithromycin 1 g PO (SD) -Metronidazole 2 g PO (SD) (Category B, safe use).	TDF/FTC + RAL bid		Not required
Children[3]	In children < 45 kg: - Ceftriaxone 25-50 mg/kg (max 250 mg) IV or IM (SD) - Azithromycin at 20 mg/kg/day POV (SD), maximum 1 g	**If >11 years and >35 Kg:** Combination tablets 245 mg TDF/200mg FTC c/24 h + Raltegravir 400mg/12h, for 28 days	Confirm vaccination history. Vaccine and gamma globulin if not immunised	
	In children > 45 kg: - Ceftriaxone 500 mg IM (MD) - Azithromycin, 1 g (MD)	**If <11 years and <35kg:** Zidovudine (AZT) + lamivudine (3TC) + Raltegravir (RAL) **Zidovudine:(4)** Dose: 9-30 Kg: 9 mg/kg/12h; >30 kg: 300 mg/12h; Introduction Suspension: 10 mg/ml Capsules: 100 and 250 mg. Tablets: 300 mg **Lamivudine:(4)** Dose: 4 mg/kg/12 h (max 150 mg/12h). From 30 Kg: 150 mg/12h; Presentations: suspension 10 mg/ml and film-coated tablets 150 and 300 mg. **Raltegravir chewable tablets:** 14-20 Kg: 100 mg/12h; 20-25 Kg. 150 mg/12h; 25-40 Kg: 200 mg/12h; >40 Kg: 300 mg; >25 Kg 400 mg /12h		

Notes:
(1)ART may require adjustment in case of renal and hepatic impairment. Baseline CBC and renal/liver function tests are required.
In case of renal failure, the recommended regimen is zidovudine/lamivudine (ZDV/3TC) + raltegravir (RAL).
The duration of the PEP will be 28 days.
The main side effects (general malaise, nausea and vomiting and diarrhoea) as well as possible drug-drug interactions will be reported.
(2) In agreement with AEP and SEIP recommendations, a single dose of azithromycin is recommended to avoid compromising adherence.
(3) In children > 9 years and adults up to 26 years who are unvaccinated or not fully vaccinated against HPV, vaccination is recommended at the time of initial screening, with follow-up doses 1-2 months and 6 months after the first dose. A 2-dose schedule (0 and 6-12 months) is recommended for persons starting vaccination before the age of 15 years.
(4) Lamivudine and zidovudine combination tablets*(Combivir*) can be used: Weight 10 - 20kg: ½ tablet c/12h, PO. Weight 20 - 35kg: ½ - 0 - 1 (tablet PO)

The risk of acquiring HIV will depend on the type of contact, the number of aggressors, the presence of traumatic injuries and the carrier status of the perpetrator(s). The administration of PEP against HIV is recommended in contacts with an estimated risk >1/1000 (receptive and insertive anal penetration, vaginal penetration with traumatic injuries), and in the context of SV in general also in vaginal penetration. PEP should be initiated within 72 hours of contact (ideally within 2 hours) and maintained for 28 days. If more than 72 hours have elapsed since contact, treatment should only be initiated in special situations and after individual assessment.

Confirmation of previous immunisations is recommended to assess the indication for additional doses, e.g. against HBV. Regarding human papillomavirus (HPV) vaccination, despite the lack of consensus in the scientific community, based on the risk-benefit balance, it is recommended that the indication for immunisation against HPV be considered according to age **(A-III**).

7.5 Follow-up

Follow-ups are opportunities to detect possible infections acquired during or after the assault, complete vaccination schedules and monitor adherence to treatments, especially PEP. If STI sampling is taken, the first follow-up visit should be early - preferably within one week of the event - for confirmation of results and appropriateness of treatment. If no treatment was administered at the time of the initial assault, STI testing should be performed 1-2 weeks after the event, due to the incubation periods of the microorganisms. In patients where tests are negative and prophylaxis was performed but the offender's status is unknown, follow-up for HIV and syphilis should be done at 6 weeks and at 3 and 6 months A-III.[10]

Upon discharge from hospital, a follow-up will be scheduled for specific consultations, which should include STI assessment and psychological support. In the STI assessment, repeat serological testing, other diagnostic tests if symptoms are present, and pregnancy testing, if appropriate, will be considered.

7.6 Clinical and forensic medical report

On discharge from hospital, the professionals involved in the examination shall draw up a clinical report, which shall be as complete as possible, objective, descriptive and shall reflect the procedures carried out, the treatments administered and any follow-up to be considered. It should be state that the interview and medical examination were carried out in the presence of the forensic doctor. The clinical report shall be coded. It is important that the protocols in place ensure that the clinical report reaches the forensic doctor. The forensic medical report for the Court will be made by the medical examiner.

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CHAPTER 8

STIs IN CHILDREN AND ADOLESCENTS

STIs in children and adolescents

KEY MESSAGES

1. The detection of an STI in a pre-pubertal child requires ruling out sexual violence as a mechanism of transmission.

2. Investigation of possible sexual violence against children **should be carried out by expert professionals.**

3. Adolescents are particularly vulnerable to STIs due to behavioural and biological factors.

8.1 STIs in children

The detection of an STI in a pre-pubertal child requires a detailed study, in which child sexual violence must be ruled out first and foremost, although other forms of transmission such as perinatal or accidental, self- or hetero-inoculation must be considered.[1]

Certain infections (e.g. non-ophthalmic gonorrhoea, syphilis, HIV, *Chlamydia trachomatis* infection and trichomoniasis), if acquired after the neonatal period, strongly suggest sexual contact (once possible transfusion and perinatal transmission in the case of HIV have been ruled out). [1-4] In addition, the diagnosis of the infection in the mother should not always be assumed to be the mode of transmission to the neonate and does not exclude the possibility of child sexual violence.[2] For other diseases (e.g: HSV, HPV, anogenital warts, and vaginosis), the association with sexual contact is less clear, but in any case requires individual assessment (see table 1).[1-4] Regarding *Mycoplasma genitalium*, current scientific evidence does not allow us to establish whether or not it is sexually transmitted in pre-pubertal children, so more studies on the prevalence and the importance of detecting *M. genitalium* in this age group are needed.[2]

Table 1. Implications of the presence of sexually transmitted or sexually associated infections for the diagnosis and reporting of sexual violence among infants and pre-pubertal children[1,3]

INFECTION	EVIDENCE OF SEXUAL VIOLENCE
*Neisseria gonorrhoeae**.	Diagnosis.
Syphilis*.	Diagnosis.
HIV**.	Diagnosis.
*Chlamydia trachomatis**.	Diagnosis.
*Trichomonas vaginalis**.	Diagnosis.
Anogenital herpes.	Suspected ¥.
Anogenital warts*.	Suspected ¥.¶
Anogenital *molluscum contagiosum*.	Inconclusive.
Bacterial vaginosis.	Inconclusive.

*If perinatal acquisition and/or vertical transmission is ruled out or unlikely.
**If perinatal or transfusion acquisition is ruled out or unlikely.
¥ Unless there is a clear history of self-inoculation.
¶ Lesions appearing for the first time in children over the age of 5 are more likely to be due to sexual transmission.

The prevalence of STIs in children who have experienced sexual violence depends on the prevalence of STIs in the population, the type of sexual activity or contact, the presence or absence of injury to the genital tract (trauma increases probability to infection), the sexual maturity of the child (greater biological susceptibility to STIs due to the physical and immunological immaturity of the genital tract in younger children) and the use or non-use of barrier methods.[2]

The investigation of possible sexual violence among children who have an infection that may have been sexually transmitted should be carried out in accordance with the recommendations of experienced and trained professionals in all elements of the assessment of child sexual violence.

Assessment of STIs in pre-pubertal children who are victims of a possible episode of sexual violence should be done on an individual basis, as well as sampling (see Chapter 7), post-exposure prophylaxis (see Chapter 7) and treatment (see relevant chapters). For the management of psychosocial or legal aspects related to child sexual violence, see Chapter 7.

8.2 STIs in adolescents

STIs are frequent in adolescents and the incidence in this age group is increasing in our environment, as in the rest of the age groups. Women aged 15-19 years are the group with the second highest incidence rate of gonococcal infection and *C. trachomatis* infection, only behind women aged 20-24 years.[1]

Adolescents are at increased risk of acquiring STIs due to behavioural and biological factors. Behavioural factors include age at first sexual encounter, having multiple sexual partners and/or new sexual partners, or sexual partners who are also having sex with others, inconsistent use of barrier methods, and use of alcohol and other drugs (although this factor may be associated with poor contraceptive use or multiple partners rather than serving as an independent marker of risky behaviours).[2]

On the other hand, several biological factors have been hypothesised to influence adolescent girls' susceptibility to STIs. One such factor is cervical ectropion or cervical immaturity, which refers to the area of the ectocervix that is covered by columnar epithelium after puberty. The columnar epithelium is thought to be more susceptible than the squamous epithelium (which replaces the columnar epithelium as it matures) to sexually transmitted microorganisms such as *N. gonorrhoeae*, *C. trachomatis* and HPV. Adolescent girls' susceptibility to STIs may also be influenced by the composition of the cervical and vaginal microbiome, which plays an important role in vaginal immune and inflammatory responses, and may be variable after puberty and first sexual experiences.[2,3]

Adolescents need to be guaranteed easy access to community health services in relation to sexual health[4],and confidentiality must be protected. It is recommended that sex education and risk reduction elements be included in the adolescent's consultation.[4]

In Spain, the age of medical consent is set at 16 years of age; between 12 and 15 years of age (inclusive), the paediatrician will assess the degree of maturity of the minor, and may classify them as a "mature child". In this case, the child can both agree to testing and treatment and decide whether or not to inform their family.[5]

For sampling, diagnostic techniques and treatment, see the relevant chapters.

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