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*Association for Genito-Urinary
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*International Union against Sexually
Transmitted Infections (IUSTI)*

European STD Guidelines

Approved by the European Branch of the
International Union against Sexually Transmitted
Infections and the European Office of the
World Health Organization

*EDITOR-IN-CHIEF FOR THE EUROPEAN
STD GUIDELINES PROJECT*

Keith Radcliffe



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International Journal of STD & AIDS

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The *International Journal of STD & AIDS* publishes clinically oriented papers on both the traditional sexually transmissible diseases (STD) and the acquired immunodeficiency syndrome (AIDS) which contribute to the advancement of knowledge in these fields. Contributions in the following categories are published: editorial reviews, original articles, case reports, papers on the history of the specialty, book reviews and letters to the Editor. All manuscripts are reviewed by independent referees, and the final decision on acceptance or rejection remains with the Editor.

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This should contain (1) the full title of the paper; (2) a short title of not more than 40 characters for page headings; (3) the initials and last names of all authors plus up to 2 qualifications for each; (4) the department(s) and the institution(s) where the work was carried out; (5) the name and address of the author responsible for correspondence about the manuscript and proofs; (6) a summary (not exceeding 150 words); (7) a list of up to 5 keywords for indexing purposes (where possible, these should be from the Medical Subject Headings list of the *Index Medicus*).

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All papers should carry a Summary not exceeding 150 words, which should state the main purposes of the study, the basic procedures used and the most important conclusions drawn; numerical data should be included. The rest of the paper should be divided into sections headed Introduction, Methods, Results and Discussion. If human investigations are being reported, the consent of patients and approval of the protocol by an ethical committee should be confirmed.

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Abbreviations. A guide for medical and scientific editors and authors, 5th edn. London: Royal Society of Medicine Press, 1994.)

Acknowledgements

Only the help of those who have made substantial contributions to the study and/or preparation of the paper should be acknowledged. The source(s) of grant support, equipment and drugs should be included.

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Only essential references should be included, and authors should verify them against the original documents. The 'Vancouver' style is used: references should be identified in the text by superior arabic numerals, and be numbered and listed consecutively at the end of the manuscript in the order in which they are first cited in the text.

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22 Mindel A, Tovey SJ, Timmins DJ, Williams P. Primary and secondary syphilis, 20 years' experience. 2. Clinical features. *Genitourin Med* 1989; 65:1-3

23 Acheson D. *AIDS*. London: Royal Society of Medicine, 1988

24 Hilleman MR. Perspectives in the quest for a vaccine against AIDS. In: Bolognesi D, ed. *Human Retroviruses, Cancer, and AIDS. Approaches to Prevention and Therapy* (UCLA Symposia on Molecular and Cellular Biology, New Series, vol. 71). New York: Alan R Liss, 1988;291-311

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Introduction

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WHY HAVE THESE GUIDELINES BEEN DEVELOPED?

The short answer would be, in the hope that by their production and dissemination, these guidelines will help to improve the management of sexually transmitted diseases (STD) in Europe, by providing:

- Healthcare workers with evidence-based recommendations
- An aid to the development of local and/or national guidelines where these do not already exist
- A tool for undergraduate and postgraduate education
- An indication of the lacunae in current evidence as a guide to future research priorities
- A resource for policy-makers and funders of healthcare.

Most healthcare workers believe that patient care will be improved if their practice is based on the best available evidence¹, but although some European countries have produced such guidelines in this branch of medicine at the national level²⁻⁵, most apparently have not.

There are a number of reasons why the time appears right for this first attempt at such an exercise at the European level.

First is the increasingly globalized nature of the world in which we must all live, work and practice our craft. In Europe this is manifested most clearly by the increasing political and economic importance of the European Union, which is likely to increase considerably in size in the medium term.

Second are the epidemics of HIV and STD in the countries of Eastern Europe and in the newly independent states (NIS) of the former Soviet Union from 1990 onwards^{6,7}. Although the syphilis epidemic may have abated somewhat since 1996/1997, the HIV epidemic has not⁸. These epidemics are attested to by a plethora of epidemiological data. By way of illustration, more new cases of HIV infection occurred in the Russian Federation during the year 2000 than in all previous years combined⁹. Although these cases are currently largely confined to intravenous drug users there are some suggestions that wider sexual spread may

be occurring¹⁰, and certainly such spread cannot be ruled out now or in the future. Similarly for other STD, between 1988 and 1996 the syphilis rate in Russia rose a staggering 62-fold, with levels in 1998 estimated to be between 200 and 500 times greater than in Western European countries¹¹. Since then, reported levels have stabilized or declined in the NIS, but this may be as much, or more, due to a shift from public to private sector treatment, resulting in less reliable notification¹⁰, than to any real decline in the incidence of infection. These high rates of STD are both a major public health problem in their own right and also a potentially important co-factor in the sexual transmission of HIV in these countries¹⁰. It is therefore no surprise that calls have been made for appropriate measures to be taken, including the promotion of international best practice in the management of STD¹⁰⁻¹². On this latter point it is hoped that these guidelines may have a contribution to make.

HOW HAVE THESE GUIDELINES BEEN DEVELOPED?

In 1998 at the 15th European IUSTI Congress on STD and AIDS in Göteborg, Sweden, the European Branch of IUSTI and the European Office of the WHO accepted a proposal made by Dr van Voorst Vader (Chief Editor, Netherlands STD Guidelines, 1997) to develop STD management guidelines for Europe. Dr Radcliffe (Chief Editor, United Kingdom STD Guidelines, 1999) agreed to join the project, initially as Co-editor, and subsequently as Editor-in-Chief.

Editorial and International Advisory Boards were subsequently established and experts from a number of European countries were approached and commissioned to produce first drafts of management guidelines. These were amended in the light of comments received from board members and second drafts produced as a result of consensus reached at a meeting of the Editorial Board.

These drafts were then placed on the IUSTI website [www.iusti.org] for the period February to April 2001 inclusive, with facility for comments to be fed back to the Editorial Board. The consultation exercise was publicized through the network of national representatives of the European Branch of IUSTI. In addition, comments on particular guidelines were actively solicited from acknowledged

experts in the areas concerned and from Dr Meheus in his capacity as a member of the WHO Expert Committee on STD. Final versions of the guidelines were then agreed at another consensus meeting of the Editorial Board.

The guidelines now appear in this supplement to the *International Journal of STD & AIDS* as the official journal of the IUSTI. Each member of this parent organization will therefore receive a copy of the guidelines. Furthermore, additional copies will be disseminated via the European branch of IUSTI and the European Office of the WHO. They will also be accessible at the IUSTI [www.iusti.org] and WHO websites [www.who.dk].

No claim is made that these guidelines represent the final word on the management of these conditions. Although every effort has been made to guard against it, errors of commission or omission may have occurred. In addition, there will obviously be a need to continually review and update them in the light of new knowledge and advances, if they are to remain useful beyond the short term. Suggestions for improvement from whatever source will always be welcomed by the Editorial Board.

To close, we should like to express our gratitude to all the authors and board members for making this project a reality, many of whom were obliged to work other than in their mother tongue. Particular thanks are due also to the IUSTI webmaster, Dr C Miller, to the pharmaceutical companies 3M and Stiefel for meeting the costs of publication through unrestricted educational grants, and last but not least to Dr Radcliffe's secretary Ms S Daisley for her invaluable administrative and clerical support throughout.

APPENDIX

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PROCEDURAL ASPECTS

European guideline for the organization of a consultation for sexually transmitted diseases

P C van Voorst Vader¹ and K W Radcliffe²

¹University Hospital, Groningen, The Netherlands and

²Whittall Street Clinic, Birmingham, UK

Note

This guideline needs to be read in conjunction with the other European guidelines on specific infections and syndromes.

PERSONNEL

A consultation for sexually transmitted diseases (STD) may involve the following staff.

- Administrative
- Nursing
- Medical—various disciplines, including: gynaecology, urology, general practice/family medicine, as well as dermato-venereology/genitourinary medicine. Also, in cases of alleged sexual assault, physicians qualified/experienced in forensic medicine may need to be involved for legal reasons
- Laboratory
- Other personnel responsible for contact tracing/partner notification and health promotion interventions.

ORGANIZATIONAL CONSIDERATIONS

The following issues need to be addressed:

- Obtaining and recording patient-specific information to allow the case to be tracked through the clinic system and to ensure results of investigations can be reliably linked to the correct person, e.g. name, date of birth, contact details (address, telephone number), usual medical practitioner. Exact details will depend on the organization of the individual clinic as well as the national healthcare system
- Financial—care (including any prescribed medications) may be: completely free, subsidized or recoverable from private insurance.

This will obviously depend on the national healthcare system.

ETHICAL CONSIDERATIONS

The following issues need to be addressed:

- Confidentiality is very important to persons consulting about suspected STD. Clinics should have clear policies on confidentiality, which are understood by all staff. Patients should be aware of any limits to confidentiality. This will vary between different countries depending on: the requirements of the healthcare system; the legal system; and the agreed professional ethical standards
- Examination, investigation and management of such persons should only be undertaken with the informed consent of the individual concerned. This will necessitate giving the person information on the likely benefits and risks in an appropriate form. If this is not feasible, e.g. children, mental incapacity, then interventions should only be carried out if they will be to the direct benefit of that person.

Note

Ethical considerations such as these will inevitably be affected by different countries' legal systems, professional ethical standards and cultural norms. However, many European countries are also signatories to the Council of Europe's Convention on Human Rights and Biomedicine, which guarantees patients' rights to informed consent (Articles 5 and 6), and privacy (Article 10), while recognizing that it may sometimes be necessary to restrict these rights, 'in the interests of public safety, for the prevention of crime, for the protection of public health or for the protection of the rights and freedoms of others' (Article 26)¹.

HISTORY

To include:

- Physical symptoms
- Previous diagnoses of STD

Correspondence to: Dr P C van Voorst Vader, University Hospital, Groningen, The Netherlands
E-mail: p.c.van.voorst.vader@derm.azg.nl

- Sexual history, to include: details of recent sexual partnerships, types of sexual contact engaged in, whether barriers were used consistently and reliably
- Symptoms and diagnoses in sexual partner(s)
- Past general medical history
- Current medications (including recent use of antimicrobials)
- Known allergies to medications
- Specific risk factors for the acquisition of HIV and hepatitis B virus infections
- Additionally in females: obstetric, menstrual, contraceptive and, if relevant, cervical cytological screening history.

INDICATIONS FOR CARRYING OUT STD EXAMINATION AND SCREENING

- Diagnosis of any STD, including: anogenital warts, genital/perigenital molluscum contagiosum, scabies, pediculosis pubis, HIV infection, hepatitis B virus infection
- Risk behaviour for STD-acquisition, especially unprotected penetrative sexual intercourse with: recent new sexual partner, multiple sexual partners, partner(s) believed to have had concurrent sexual relationship(s), partner recently diagnosed as having STD, partner reporting symptoms suggestive of STD (see below)
- Involvement in commercial sex work (prostitution), either as a worker or as a client
- Alleged sexual abuse or assault
- Symptoms or physical signs suggestive of possible STD:
 - In females:
 - Upper genital tract symptoms suggesting possible pelvic infection: pelvic pain, abnormal menstruation, dyspareunia,
 - Vaginal discharge
 - In males:
 - Urethral discharge
 - Dysuria
 - Circinate balanitis
 - Testicular pain
 - In both sexes:
 - Genital ulceration
 - Rectal pain or discharge (associated with a history of receptive anal intercourse)
 - Mono/pauci-articular arthritis
 - Conjunctivitis
- Sexual contact with person with any of the above symptoms/syndromes
- Planned instrumentation of the cervix in females, especially induced abortion, also consider prior to insertion of intra-uterine device, or planned *in vitro* fertilization.

PHYSICAL EXAMINATION

To include:

- Examination of anogenital area in males and females
- Speculum examination in females
- Bi-manual pelvic examination in females if upper genital tract symptoms (see earlier)²
- Proctoscopy in males and females if indicated by symptoms or sexual history
- Extend to other systems if necessary as indicated by symptoms.

LABORATORY INVESTIGATIONS

Routinely in all patients for:

- *Chlamydia trachomatis*
- *Neisseria gonorrhoeae*
- Syphilis
- HIV infection.

When indicated by symptoms, sexual history or physical examination, for:

- Bacterial vaginosis
- *Candida albicans*
- *Trichomonas vaginalis*
- Ano-genital herpes
- Scabies
- Pediculosis pubis
- Chancroid
- Lymphogranuloma venereum
- Granuloma inguinale
- Hepatitis B virus infection.

Notes

Decisions on which investigations to perform should also be informed by:

- Local epidemiological data
- The clinical setting.

DIAGNOSIS AND PREVENTION

- Wherever feasible this should preferably be based upon the results of laboratory investigations for the following reasons:
 - *Asymptomatic infections* are common and can only be excluded by appropriate laboratory investigations
 - *Diagnosis*: to increase the reliability of the diagnosis which may have serious implications for the patient and their sexual partners(s) and/or children
 - *Therapy*: to allow more appropriate therapy, especially where antimicrobial resistance testing can be performed
 - *Follow-up*: to decide whether follow-up testing may be indicated (so-called 'tests of cure')

— *Epidemiology*: to allow greater accuracy in the notification of infections, and in the return of epidemiological data to public health agencies.

- It may be possible to give a microbiologically-confirmed diagnosis at the initial consultation by the utilization of microscopy or other 'near-patient' technologies
- If tests have poor positive or negative predictive values then patients should be made aware of the limitations of any results
- Patients should receive an appropriate and adequate explanation of their diagnosis and be given the opportunity to ask questions
- Explanation should be reinforced wherever possible by the giving of high-quality written information
- Diagnosis of an STD represents an opportunity to deliver health-promotion advice to reduce the likelihood of repeat infection with STD in the future.

TREATMENT

- Should be given at the initial consultation when:
 - A diagnosis can be made at that visit
 - Epidemiological treatment is indicated as a result of a diagnosis in a sexual partner
- Where feasible, single-dose therapy administered in the clinic under the supervision of staff maximizes compliance
- Patients should be advised of the need to avoid unprotected sexual intercourse as long as there is a real possibility of transmitting infection or becoming reinfected
- Special care is required in female patients who are known to be pregnant or breastfeeding,

and in those in whom pregnancy cannot confidently be excluded.

PARTNER NOTIFICATION

- Should be considered in all cases of confirmed STD
- Identifying which partners need to be contacted will depend on what is known of the probable incubation period and the sexual history
- Notification may be done by healthcare staff or by the index patient
- Must conform to the legal and professional ethical frameworks of the individual country.

FOLLOW UP

- Should be considered in all cases
- May be done in various ways, e.g. return visit, telephone call
- May be indicated for the following reasons:
 - To inform the patient of the results of laboratory investigations
 - To assess compliance with therapy
 - To enquire about the possible side-effects of therapy
 - To assess the results of therapy, including the need to perform 'tests-of-cure'
 - To follow-up on partner notification
 - To reinforce health promotion messages.

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PROCEDURAL ASPECTS

European guideline for testing for HIV infection

Johannes Thorvaldsen

Olafia Clinic, Oslo, Norway

INTRODUCTION

HIV testing was introduced in 1985, primarily as a tool to control the blood supply for the presence of HTLV-3, later called the human immunodeficiency virus (HIV). HIV testing is defined as the serological procedure searching for HIV antibodies (or HIV antigen/HIV-RNA) in an individual person, whether recommended by a healthcare provider or requested by the individual¹.

HIV testing remains one of the most important single measures that any society can offer in its efforts to combat HIV infection, on both an individual and a societal level.

The recent advances in the treatment of HIV disease have led to expectations of high efficacy of antiretroviral therapy. However, regardless of how recommendations to initiate antiretroviral therapy might change in the future, early diagnosis of HIV infection will remain preferable to late diagnosis².

Confidentiality and counselling before and after testing must be an integral part of the testing procedure³ and informed consent must be obtained before an HIV-test is performed.

The primary goals of testing⁴ are:

- To identify HIV-infected persons for clinical intervention or for screening purposes
- To provide pre- and post-test counselling for HIV-negative persons at risk of HIV transmission and for HIV-positive persons to reduce transmission of the virus to others
- To initiate partner notification with counselling and referral to prevention services for partners of HIV-positive persons.

INDICATIONS FOR HIV TESTING

Diagnostic HIV testing

- HIV testing of persons who may have symptoms or clinical signs of HIV infection. Few, if any, symptoms are pathognomonic for HIV infection. However, some symptoms and physical signs should make the clinician consider the possibility of primary HIV infection, such as fever, lymphadenopathy,

rash, ulceration of mucous membranes, myalgia or arthralgia. In this situation, blood tests for HIV p24 antigen or HIV-RNA are useful in making a rapid diagnosis, although it should be realized that a low-level HIV-RNA result (<10 000 copies/ml) may represent a false-positive reaction. Follow-up HIV antibody testing is indicated in all cases⁵

- Other later symptoms may also be the reason why the person seeks medical attention and signs may as well be observed by the healthcare worker during the consultation or hospitalization. Most persons with HIV infection have no symptoms at all.

The natural history of HIV infection, including both the time before the onset of symptomatic HIV disease and its signs and symptoms will be dependent on the characteristics of the individual (age, sex, genetics, previous health condition, time from transmission, mode of transmission, etc.) and of the virus (viral strain, whether syncytial producing virus or not, index person's viral load and CD4-lymphocyte level, whether the index person has received antiviral treatment or not, etc.)^{6,7}. A close description of all conceivable symptoms is hence beyond the scope of this guideline.

Voluntary HIV testing

When persons who believe that they might have been exposed to HIV, either themselves request an HIV test or are offered an HIV test by a healthcare provider.

Testing for HIV should be offered to the following individuals:

- Persons with multiple sex partners
- Persons who seek evaluation and treatment for sexually transmitted infections (STIs), particularly after diagnosis of an STI where acquisition was associated with an increased risk of HIV transmission (e.g. history of unprotected sexual intercourse)
- Presence of an unusual form of STI (e.g. chronic ulcerative anogenital herpes)
- Insufficient response to therapy for another STI^{4,8,9}
- Persons who have a history of past or present intravenous drug use

- Partners to all above-mentioned persons including partners found by partner notification
- Persons coming from or returning from high endemic HIV/AIDS areas, requesting examination for STIs and their partners
- Healthcare workers and other persons who have accidentally been exposed to body fluids, which may or may not contain HIV virus, such as blood, fluid containing visible blood or other potentially infectious fluid or tissue, such as semen and vaginal fluid, either by needle-stick injury or by inoculation onto mucous membrane or damaged skin⁴
- Persons/patients who have been the victims of criminal offences like rape or sexual abuse
- Persons who have been sexually exposed to a known HIV-positive person and where there might be indication for post-exposure prophylaxis (PEP) with antiretroviral drugs^{10,11}
- Persons who have received blood transfusion or other blood products before blood was being screened for HIV antibodies (in most countries before 1985)¹²⁻¹⁶
- Any pregnant woman regardless of risk factors, but particularly those who have one or more of the above mentioned risk factors.

SCREENING

Screening refers to the performance of a diagnostic test in asymptomatic persons with the aim that early diagnosis may lead to improved outcome and halt the spread of disease¹⁷.

Since the HIV test became available in 1985, the guiding principle of programmes aimed at reducing HIV transmission by blood transfusion has been the testing of all donated blood for HIV antibodies. Predonation written questionnaires have been shown to prevent persons who have had unsafe sex since last blood donation from donating during the window period (see later). This has resulted in a dramatic decrease in the transmission of HIV infection by blood transfusion.

Operationally, HIV screening is the systematic application of HIV testing to any of the following groups:

- All donors of blood, organs, semen, breast milk and any other human material should be screened for HIV antibodies
- All pregnant women should be offered HIV testing as early in pregnancy as possible, either as part of a national screening programme or by individual testing
- Other relevant target populations or groups should be offered HIV testing.

Regarding specific groups, The World Health Organization has clearly stated in its report on criteria for HIV screening programmes that the usefulness of such programmes must be weighed carefully against their potential deleterious effects¹.

Among the criteria that should be met in any screening programme are: validity, reliability, sensitivity and specificity of the test (resulting in acceptable, positive and negative predictive values). A positive HIV test must be confirmed, the patient notified, and treatment offered if indicated.

LABORATORY

The first test for HIV became available after the virus was identified in 1984. HIV infection is established by detecting antibodies to the virus or by detecting the viral antigens, by nucleic acid-based tests or by culture¹⁸. The standard test is serologic detection of HIV antibodies. There are two types of virus: HIV 1 and HIV 2 which show 40–60% amino acid homology. HIV 1 is divided into two groups (M and O) and group M is subdivided into sub-groups A to I¹⁹.

HIV antibody tests

- ELISA/ELA (enzyme-linked immunosorbent assay). The most commonly used test to detect HIV Ig G antibodies in the patient's serum is the EIA test. Patient HIV antibodies bind to HIV antigen in the presence of an enzyme that cleaves a colourless substrate into a colour product which subsequently is spectrophotometrically assessed²⁰. The test is readily available and inexpensive. Confirmation of an initially reactive sample with a second test using viral antigens and/or format of a different type is recommended before a confirmed positive result is reported
- Western blot. This test is designed to detect anti-HIV 1 antibodies. In addition, it allows determination of the specific antigen against which the antibody is directed, through an electrophoretic process. Although the precise criteria for what constitutes a positive Western blot test remain controversial²⁰, the test is widely used for confirmation of a positive EIA test, although this is no longer regarded as essential. The sensitivity and specificity exceed 99.9% for the combination of an EIA screening assay and confirmatory Western blot on EIA-positive specimens¹⁹.

HIV antigen tests

- HIV P-24 antigen test. This assay measures the amount of free viral protein (p-24) present in the plasma or tissue culture supernatant and again later in advanced HIV disease²⁰.

Virus culture techniques

- PBMC (peripheral blood mononuclear cells) co-culture for HIV1 isolation. Tissue culture procedure is expensive, time-consuming, labour-intensive and has variable success, so should not be used to diagnose infection.

PCR (polymerase chain reaction)

- PCR was introduced in the late 1980s, and represents a major diagnostic advance in many diseases, including HIV infection. This powerful technique can amplify target DNA or RNA existing in very small quantities (as few as one copy of HIV per 100 000 cells) through a series of binary replicative cycles
- The major problem with PCR amplification, ironically, is also its greatest strength, that is, its incredible sensitivity. Unfortunately, inadvertent contamination of reagents or target DNA can lead to false-positive results. Nonetheless, when used properly in laboratories with experienced personnel, this technique allows early detection of infection before the development of the serologic response²⁰
- Measuring viral load by quantitative PCR has become a standard procedure for staging and monitoring the response to antiretroviral therapy. This also has a role in the diagnosis of primary HIV infection, although care must be exercised (see earlier under 'Diagnostic HIV testing').

Accuracy

- Newer and more sensitive tests reduce the usual window period to 3–4 weeks¹¹, however the accuracy of HIV serology is also excellent, results being reported as positive, negative or indeterminate. Criteria for a positive test are a repeatedly positive ELISA followed by a positive Western blot. Indeterminate results most often result from a positive EIA and a single band on Western blot, usually p-24. Among the many causes of indeterminate results are seroconversion and cross-reacting alloantibodies or autoantibodies
- Patients in low-risk categories with indeterminate results are almost never infected with either HIV-1 or HIV-2¹⁹, however an indeterminate result has to be followed up by a repeat test after 3–12 weeks.

The window period

- The time delay from HIV transmission to seroconversion is usually less than 3 months (see above). Rarely, cases might have a longer window period.

HIV 2

- HIV 2 is found primarily in countries of West Africa. HIV-2 antigens are usually contained in EIA tests which will be positive if the person is infected with HIV-2.

False-positive HIV tests

- Administrative error in the clinic or the laboratory (e.g. incorrect labelling of specimens

or forms) may lead to incorrect results being given to persons undergoing HIV testing. It is therefore recommended practice that a further sample of blood be drawn from all patients on whom a positive HIV antibody test has been reported, and subjected to the same HIV antibody testing process

- By a false-positive HIV test is meant the combination of positive EIA *and* Western blot. In screening of a low-prevalence populations, a rate of false positives from 0.0004–0.0007% is found^{22,23}
- The most common cause of a false-positive test is vaccination. However, one single case has been ascribed to systemic lupus erythematosus and end-stage renal disease
- Screening patients with plasma HIV-RNA assays may also result in false-positive tests and should be confirmed with routine serology²⁴.

HIV TESTING MANAGEMENT

The most common reasons why HIV antibody tests are performed are:

- Because an HIV test is recommended by a healthcare provider
- Because an HIV test is requested by a patient. Generally, testing should be performed in all situations when requested by a patient, possibly with the exception of repeated HIV testing as a part of a risk reduction strategy^{25,26}.

All testing should be carried out on a voluntary basis and opportunities should be provided for anonymous testing²⁷ (see additional testing provisions). Any HIV testing procedure should adhere to the following principles:

- Confidentiality
- Informed consent
- Pre- and post-test counselling.

Confidentiality

Confidentiality between patient and physician has never been absolute, however, regarding the HIV testing situation, the confidentiality must be protected to the extent that it enables optimal patient care and encourages people to seek testing and counselling^{9,28}.

The confidentiality provisions will always be dependent of the legal framework in any specific country. These should be discussed with the patient and if testing is refused on grounds related to confidentiality, an anonymous test should be provided⁴.

Informed consent

- As a general rule, the consent of the patient is an essential prerequisite to medical treatment of any kind²⁹. Otherwise, personal integrity and privacy is violated³⁰

- Informed consent must be obtained before an HIV test is performed. The rationale is that HIV serology is considered an invasive test due to the enormous consequences in terms of potential discrimination in insurance, employment, healthcare and personal relationships¹⁹. The patient must be fully informed and explicit consent must be given. A general consent to treatment is not likely to be held to cover testing for HIV antibodies³
- In a clinical situation where there is an indication for HIV testing and the provider has come to the conclusion that it would be negligent on his part not to arrange for an HIV test, he is under the duty to explain the situation to the patient and seek to obtain his consent to the test being carried out in his own interest
- Few if any circumstances where consent cannot be obtained might represent exceptions to this rule. The major exception arises when the patient is unconscious and therefore unable to give consent, and knowledge of the patient's HIV status is regarded as essential for the protection of the patient's life or the preservation of his health^{29,31}.

Pre-test counselling

In spite of the advent of highly active antiretroviral treatment which has changed the prognosis of HIV disease profoundly, the implications of a positive HIV test are still far-reaching.

Comprehensive pre- and post-test counselling are an essential preparation for coping effectively during and immediately after testing³². Apart from providing the client with factual knowledge and preparing for the practical procedures, the counselling should exploit fully the opportunity for prevention of STI generally and HIV particularly.

Components of pre-test counselling

- Obtain informed consent. Some institutions require written consent. Discuss confidentiality provisions. Discuss options for anonymous testing
- Obtain a history, including detailed sexual and other types of risk behaviour, including why the patient wants an HIV test at this particular time
- Discuss the likelihood and implications of a positive, negative and indeterminate test result
- Ensure understanding of HIV transmission, safer sex behaviour and the window period
- Ensure knowledge of condom use. Include practical demonstration for both sexes if needed
- If appropriate, discuss risk reduction and need for referral to other services, e.g. drug dependency treatment, support schemes, needle exchange, etc.

- The procedure for informing the person of the result should be communicated clearly. Try to avoid communicating results at times when ongoing support may be difficult, e.g. immediately before weekends and public holidays
- Based on what you know about the person, make a realistic, client-centred, approach at behaviour modification³³.

Post-test counselling

Evidently, the majority of HIV tests are negative. However, there is general agreement upon the fact that the consultation in which the client receives his result may be a fruitful moment in underscoring some of the points from the pre-test counselling.

Components of post-test counselling

When the result is negative:

- Discuss the window period and address the need for a repeated test for those with risk behaviour later than 3 months ago
- Continue and reinforce the behaviour intervention approach, particularly addressing the need for behaviour change regarding unsafe sex or the sustainability of safer sex practise
- Post-test counselling represents an opportunity to refer persons with particular high-risk behaviour to HIV prevention and other services³⁴.

When the result is inconclusive:

- Discuss possible explanations
- For persons reporting high-risk behaviour, discuss the possibility of acute HIV infection and consider repeat testing using HIV-RNA PCR (or HIV antigen) for a quicker diagnosis of HIV infection, particularly for pregnant women who have not been previously tested
- Discuss safer sex and safe drug-use behaviour until the indeterminate result is resolved.

When the result is positive: Patients are usually distressed when first informed about a positive HIV test result. They are faced with major adaptive challenges, such as accepting the possibility of a shortened lifespan, coping with other people's reactions to a stigmatizing illness, and with developing and adopting strategies for maintaining physical and emotional health³⁵. Appropriate support should be available on-site or through referral to address the behavioural, psychosocial and medical implications of HIV infection. The following issues should be covered:

- Inform the client straightforwardly that the HIV test was positive. Wait for the client's reaction. Be supportive
- Arrange for a repeat test to confirm the result
- Make sure that the client has understood the implications of a positive test

- Address the question of whom the client wants to inform, now and later, e.g. partner(s), friends, family
- Discuss what will happen next. Does the client want to talk further at this stage or not?
- Schedule a new consultation in the near future, e.g. next day.

Experience has shown that even when the patient expected a positive result, there is still a powerful emotional reaction. Hence, it may be wise to postpone some of the information-giving to subsequent consultations:

- Inform about treatment options. Discuss anti-retroviral drugs and emphasize their ability to favourably alter disease progression
- Assess the need for psychological support or contact with other services, e.g. drug dependency, and refer as necessary
- Address how to avoid transmitting HIV to others. Discuss safe sex, use of condoms, not sharing needles, etc.
- Discuss the need for partner notification.

Regarding the seropositive woman, there are some particular issues which should be included in the counselling at an early stage⁸:

- Discuss how to avoid pregnancy
- Discuss the need for a gynaecological examination
- Discuss the implications for possible future pregnancy: the risks for the child and the need for antiretroviral therapy during pregnancy. 15–25% of infants born to untreated HIV-infected mothers are infected with HIV; antiretroviral treatment can reduce this risk to less than 8% if administered to women during pregnancy^{30,36,37}
- If already pregnant, discuss the implications (see previous point).

ADDITIONAL TESTING PROVISIONS

Anonymous testing

Both privately and publicly funded testing sites for HIV should also consider offering anonymous HIV testing along with ordinary HIV testing as part of their routine service. Persons who are anonymously tested are not required to provide their names. However, most departments will require the identity during follow-up of a person with a positive HIV test.

- Anonymous testing may contribute to early HIV testing and earlier entry into medical care³⁸
- A comparative trial has shown that those who prefer anonymous testing are young and single people and are more likely to have acquired a new regular partner during the last year³⁹

- Some studies^{40–42} suggest that men who have sex with men are more likely to seek HIV testing when it is offered anonymously
- Persons with lower income and less education are more likely to be willing to be tested for HIV if the results could be known only to them⁴³.

Rapid HIV testing

Tests have been developed in which a clinician can perform a screening assay on a blood sample and provide test results within 20 minutes. Patients with a negative test do not have to have the result confirmed, however, a positive test must be confirmed.

- Patients seeking HIV testing in an STI clinic or another test site might be offered a choice between an ordinary HIV test and a rapid test. In an STI clinic setting it was deemed practical and did not adversely affect patient flow. Counselling can be done while the test is being performed. It is cost-effective^{44,45}
- The acceptability of these tests to both clients and providers is high⁴⁶ and with a sensitivity of 100%, specificity of 99.1–99.5% and a positive predictive value of 87–88%^{47,48}, the test is highly valid
- Rapid HIV antibody tests allow provision of results and result-specific counselling on the day of the initial visit and might have the potential to increase the efficacy of HIV counselling and testing⁴⁵
- Rapid HIV testing might improve the way potential consumers view the product of early HIV diagnosis. Client and provider convenience might be increased by negating the need for a follow-up visit and will probably increase the inclination to be tested. It has been successfully implemented not only in genitourinary clinics, but also at other sites^{49,50}.

Partner notification/contact tracing

Partner notification or partner referral is a cornerstone of STI programmes worldwide⁵¹. The rationale for partner notification is that early diagnosis and treatment of HIV infection may reduce morbidity and mortality, and provides the opportunity to reduce high-risk behaviour.

- Sexual partners and those who share needles with HIV-positive persons, and who are or have been at risk for being infected with the virus, should be routinely counselled and tested for HIV antibodies⁵².

Generally used approaches to inform partners of index patients:

- Patient referral. The provider and the patient agree that the patient will notify his or her own partners

- Provider referral. The provider agrees to inform the partner(s). The issue of under what circumstances, if any, the name of the index patient will be disclosed needs to be clearly discussed, and needs to take into account the professional, ethical and legal situation in the individual country.

Partner notification is a challenge for any health-care system. The attitude towards people with risk behaviour regarding HIV, social values, the ability to communicate and to what degree the patient has trust in the system, are factors that are crucial to the success of any partner notification programme.

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MANAGEMENT OF SPECIFIC INFECTIONS

European guideline for the management of syphilis

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INTRODUCTION

Syphilis is classified as acquired or congenital. Acquired syphilis is divided into early and late syphilis. Early syphilis: primary, secondary and early latent (Centers for Disease Control [CDC]: acquired <1 year previously¹; World Health Organization [WHO]: acquired <2 years previously²). Late syphilis: late latent (CDC: acquired ≥1 year previously¹; WHO: acquired ≥2 years previously²), tertiary, including gummatous, cardiovascular and neurosyphilis (the latter two are also sometimes classified as quaternary syphilis). Congenital syphilis is divided into early (first 2 years of life) and late (apparent later in life), which includes the stigmata of congenital syphilis.

DIAGNOSIS

Clinical features

Incubation period: 10–90 days before a chancre (primary syphilis) develops, in symptomatic patients. Secondary syphilis develops 3–6 weeks after the appearance of the chancre.

Primary syphilis: an ulcer (chancre), usually with regional lymphadenopathy. The ulcer is single, painless and indurated with a clean base, discharging clear serum, in the anogenital region. Occasionally it may be atypical: multiple, painful, purulent, destructive, extragenital (including syphilitic balanitis of Follmann³). Any anogenital ulcer is syphilitic unless proven otherwise.

Secondary syphilis: multisystem involvement due to bacteraemia, which may recur up into the second year after infection. Generalized non-itchy polymorphic rash often affecting the palms and soles, condylomata lata, mucocutaneous lesions, generalized lymphadenopathy. Less commonly patchy alopecia, anterior uveitis (i.e. ocular syphilis, which may also cause scleritis, iritis, retinitis, papillitis, optic neuritis), meningitis, cranial nerve palsies, hepatitis, splenomegaly,

periostitis and glomerulonephritis. The rash may be itchy, particularly in dark-skinned patients⁴.

Latent syphilis: positive serological tests for syphilis with no clinical evidence of treponemal infection. Arbitrarily classified as early if acquired <1 year previously and late if acquired ≥1 year previously.

Late syphilis includes:

- Gummatous syphilis: typical nodules/plaques or ulcers
- Neurosyphilis: meningovascular, parenchymatous (general paresis, tabes dorsalis), asymptomatic (abnormal cerebrospinal fluid (CSF))
- Cardiovascular syphilis: aortitis (asymptomatic), angina, aortic regurgitation, coronary ostia stenosis⁵, aortic aneurysm (mainly thoracic).

Laboratory

Treponema pallidum from lesions or infected lymph nodes in early syphilis, demonstrated by:

- Darkfield microscopy
- Direct fluorescent antibody test—for oral or other lesions where contamination with commensal treponemes is likely
- Polymerase chain reaction (PCR)^{6,7}.

Serological tests for syphilis include^{8,9}:

- Reaginic tests (cardiolipin/non-treponemal tests): Venereal Disease Research Laboratory test (VDRL), rapid plasma reagin test (RPR) and variants
- Specific tests (treponemal tests): *T. pallidum* haemagglutination assay (TPHA), microhaemagglutination assay for *T. pallidum* (MHA-TP), *T. pallidum* particle agglutination test (TPPA), fluorescent treponemal antibody absorption test (FTA-abs test), treponemal enzyme immunoassay (EIA)/IgG (e.g. Captia), IgG immunoblot test for *T. pallidum*
- Specific anti-*T. pallidum* IgM antibody tests: 19S-IgM-FTA-abs test, IgM-immunoblot for *T. pallidum*, anti-*T. pallidum* IgM-antibody test using the EIA method (Captia EIA). Present indication for IgM antibody test screening for congenital syphilis and recent infection.

Preliminary screening tests^{10,11}:

- TPHA, MHA-TP or TPPA are the best single screening tests. VDRL or RPR are sometimes also performed (in addition)
- EIA/IgG-test is an alternative screening test
- FTA-abs test or EIA-IgM may be the first test to be positive if primary syphilis is suspected; the first test is reactive in 70–90% of cases⁸.

Confirmatory tests if any screening test is positive^{10,11}:

- Treponemal EIA, FTA-abs test (i.e. another treponemal test, e.g. TPHA if EIA is used for screening, EIA if TPHA is used for screening)
- IgG-immunoblot for *T. pallidum* if suspected false-positive TPHA/MHA-TP and/or FTA-abs test
- Always repeat positive tests to confirm results.

Test for serological activity of syphilis and for monitoring the effect of treatment:

- VDRL-test or RPR-test (or variants, i.e. other cardiolipin/non-treponemal tests).

Laboratory: false-negative syphilis serology^{8,9}

- A false-negative reaginic (cardiolipin) test may occur in secondary syphilis due to the prozone phenomenon from using undiluted serum
- A temporary negative reaginic (cardiolipin) test has occasionally been reported in secondary syphilis and in patients with concomitant HIV infection (reactive on subsequent testing).

Laboratory: false-positive syphilis serology^{8,9}

- Biological false-positive (BFP) reaginic (cardiolipin/non-treponemal) tests can be divided as acute (<6 months) and chronic (≥6 months). Acute BFP may be seen in pregnancy, post-immunization, recent myocardial infarction and in many febrile infective illnesses. Chronic BFP may be seen in injecting drug users, autoimmune diseases, leprosy, chronic liver pathology and old age. Occasional biological false-positive treponemal tests (FTA-abs test more than TPHA/MHA-TP) may be seen in autoimmune diseases, HIV infection and during pregnancy and can be excluded with the IgG immunoblot test for *T. pallidum*
- False positive syphilis serology (treponemal and cardiolipin/non-treponemal) is also found in endemic treponematoses and borreliosis. The treponematoses are caused by bacteria from the group of spirochaetes, which include *Borrelia*, *Spirochaeta*, *Leptospira*, *Cristispira* and *Treponema*, such as:
 - *T. pallidum* (venereal syphilis and endemic syphilis)
 - *T. pertenue* ('yaws'/framboesia tropica)
 - *T. carateum* (pinta)

The antibodies to endemic treponematoses such as endemic syphilis, framboesia (yaws) and pinta cannot be distinguished from the antibodies induced by *T. pallidum*. A person with positive syphilis serology from a country with endemic treponematoses should be investigated and treated as for syphilis as a precautionary measure, unless previously adequately treated for syphilis

- The false-positive syphilis serology caused by the spirochaete *Borrelia burgdorferi* results from the antigenic relationship between *T. pallidum* and *B. burgdorferi*, since both are spirochaetes. This can usually be avoided by routine preincubation with *T. phagedenis*. False-positive treponemal reactions frequently occur however with the FTA-abs test. Now that the genome of *T. pallidum* has been mapped completely¹², new more specific test for *T. pallidum* may be developed
- False-positive syphilis serology in pregnancy:
 - False-positive cardiolipin/non-treponemal and treponemal reactions can occur in pregnancy, with treponemal tests the FTA-abs test is the one which may be false-positive
 - If a pregnant woman has been adequately treated for syphilis prior to the current pregnancy, there are no rational arguments for a so-called safety treatment. But in the case of a possible new syphilitic infection (recheck sexual partner) and also if there is any doubt about the adequacy of previous therapy, one should not hesitate to proceed with treatment.

Laboratory tests to confirm or exclude neurosyphilis^{1,13,14}

- Lumbar puncture for examination of CSF is indicated in patients with^{1,14}:
 - Clinical evidence of neurological involvement
 - Ocular, cardiovascular or gummatous syphilis
 - Concomitant HIV infection

Note: Lumbar puncture for CSF examination is an option in non-HIV-infected patients with late latent syphilis or in whom the duration of latent syphilis infection is unknown. This examination should exclude asymptomatic neurosyphilis, although the benefit may be marginal¹⁵ and the need minimal, as the risk of developing symptomatic neurosyphilis after standard parenteral treatment appears to be small in such patients^{14,16–18}, although it has been described¹⁸.
- Examination of CSF: TPHA/MHA-TP/TPPA (qualitatively), FTA-abs test (qualitatively), VDRL test (quantitatively), total protein,

albumin level, number of mononuclear cells. Quantitative TPHA/MHA-TP and measurement of IgG and IgM level in CSF can also be performed, together with measurement of albumin, IgG and IgM level in serum

- Extra parameters in CSF: IgG-index, IgM-index, albumin quotient. The IgG-index decreases after adequate therapy, but may remain abnormal, as does the TPHA-index and the albumin quotient. IgM-index and the number of mononuclear cells in the CSF should become negative or normal within 1–2 years. The VDRL test in CSF may or may not become negative following therapy. The use of the different TPHA-indexes and ITPA-indexes has been controversial^{13,19}. The value of the PCR for determination of the presence of *T. pallidum* antigen(s) in CSF and diagnosis of neurosyphilis is rather disappointing^{13,14}.

—IgG-index (parameter for intrathecal IgG synthesis, normal value: <0.70)^{13,18}:

$$\frac{\text{IgG level (mg/l) in CSF}}{\text{IgG level (mg/l) in serum}} : \frac{\text{albumin level (mg/l) in CSF}}{\text{albumin level (mg/l) in serum}}$$

—IgM-index (parameter for intrathecal IgM synthesis, normal value: <0.07)^{18,19}:

$$\frac{\text{IgM level (mg/l) in CSF}}{\text{IgM level (mg/l) in serum}} : \frac{\text{albumin level (mg/l) in CSF}}{\text{albumin level (mg/l) in serum}}$$

—Albumin-quotient (parameter for disturbance of blood–brain barrier, normal value: <7.8)^{13,18,19}:

$$\frac{\text{albumin level (mg/l) in CSF}}{\text{albumin level (mg/l) in serum}} \times 1000$$

- TPHA-index, according to Luger¹³ (parameter for intrathecal synthesis of anti-*T. pallidum*-specific IgG). This TPHA-index was shown to have a specificity of 100% and a sensitivity of 98.3% in one study involving 60 HIV-seronegative symptomatic neurosyphilis patients and controls¹³. This leaves the question of reproducibility of the CSF-TPHA (appears to be good), the sensitivity of the index in oligo- and asymptomatic neurosyphilis and the influence of HIV-infection. Confirmation of the findings of Luger *et al.* has been limited so far¹³.

$$\frac{\text{CSF-TPHA titre}}{\text{Albumin quotient}}$$

- Criteria for the diagnosis of neurosyphilis^{13,14}:

TPHA/MHA-TP and/or FTA-abs test positive (in CSF)
 and
 Increased number of mononuclear cells (>10/mm³ in CSF)
 plus
 IgG-index ≥0.70 and/or IgM-index ≥0.10 (in CSF)
 or
 positive VDRL test (in CSF).

- Additional criteria in HIV-seronegative patients suspected of symptomatic neurosyphilis: TPHA-index (according to Luger, see above) >70 and <500: compatible with neurosyphilis; TPHA-index (according to Luger, see above) >500: definite neurosyphilis¹³

- Other considerations:

— Finding in CSF a positive TPHA, an increased number of mononuclear cells and a raised IgG- and/or IgM-index only provides circumstantial evidence for the diagnosis of neurosyphilis. A positive VDRL test in CSF is seen as more direct evidence of neurosyphilis

— The number of mononuclear cells in CSF can be normal in neurosyphilis, especially in parenchymatous neurosyphilis (tabes dorsalis, general paresis)^{18,19}

— The VDRL test in CSF can be negative in neurosyphilis^{13,18,19}

— A positive TPHA/MHA-TP/TPPA or FTA-abs test in CSF by itself does not confirm the diagnosis of neurosyphilis, but a negative treponemal CSF test excludes neurosyphilis¹³

— Tests may be performed for the presence of HIV-RNA or HIV-p24 Ag in CSF of HIV-infected individuals, which indicate HIV-infection of the central nervous system

— The criteria outlined above have not generally been validated in HIV-seropositive patients.

Screening test to exclude symptomatic cardiovascular syphilis

- Chest radiograph

Investigation for ocular syphilis

- Indicated if ocular complaints are present
Note: Ocular assessment (slit lamp) may be helpful to differentiate between acquired or congenital ocular syphilis (interstitial keratitis) in cases of latent infection of uncertain duration.

MANAGEMENT^{5,14,16,20}

General

- A treponemicidal level of antimicrobial should be achieved in the serum, and in the CSF in the case of neurosyphilis. A penicillin level of >0.018 mg/l is considered treponemicidal, but is substantially lower than the maximally effective *in vitro* level of concentration, which is far higher (0.36 mg/l)^{5,16}

- Duration of treponemicidal level of antimicrobial should be at least 7–10 days to cover a number of division times (30–33 hours) of treponemes in early syphilis with a subtreponemicidal interval of not more than 24–30 hours⁵. Longer duration of treatment is needed as the duration of infection increases (more relapses were seen in that stage after short courses of treatment), possibly because of more slowly dividing treponemes in late syphilis. Treponemes have shown to persist despite apparently successful treatment²⁰. The significance of this finding, if any, is unknown
- Long-acting benzathine penicillin 2.4 million units provides a treponemicidal penicillinaemia for up to 3–4 weeks (21–23 days)^{5,21}. With daily parenteral treatment with procaine penicillin a 'safety margin' is provided by giving courses lasting 10–14 days in early syphilis and 10–21 days in late syphilis. However, well controlled clinical data are lacking on the optimal dose, duration of treatment and long-term efficacy of antimicrobials, even of penicillin, which has been used most extensively¹⁶
- The recommendations are based mainly on laboratory considerations, biological plausibility, practical considerations, expert opinion, case studies and past clinical experience¹⁶
- Parenteral rather than oral penicillin treatment has generally been the treatment of choice because parenteral therapy is supervised with guaranteed bioavailability. Oral fenoxymethylpenicilline is an option however²², and amoxicillin given orally in combination with probenecid resulted in treponemicidal CSF penicillin levels^{23,24}
- Non-penicillin antibiotics that have been evaluated are tetracyclines, including doxycycline, which is the preferred tetracycline with penetration into the CSF^{16,20,25}, and erythromycin, all taken orally. Erythromycin is least effective and does not penetrate the blood-brain or placental barriers well²⁰. Newer antitreponemal regimens include oral azithromycin^{16,26–28} and intramuscular or intravenous ceftriaxone^{29,30}. The latter has good CSF penetration. More data are required, however, before either can be generally recommended, although both may be preferable to erythromycin and tetracycline
- The host immune response is important as 60% of untreated patients go through life without developing late complications³¹. CSF involvement is common in early syphilis^{32,33}. Although both benzathine penicillin and standard regimens of parenteral procaine penicillin do not achieve treponemicidal CSF levels^{14,16,34,35} the prevalence of late syphilis, including neurosyphilis, remains low, indicating that treatment is effective and suggesting that host immune responses in early syphilis play an essential part. However, standard treatment with parenteral benzathine penicillin has been associated with failure in pregnant women^{36–38}
- Benzathine penicillin is available as Penidural[®] and is widely used because of ease of treatment. Using lidocaine solution as part of the solvent reduces the pain associated with injection and may improve compliance. Compliance with daily intramuscular injections with procaine penicillin has been good in the UK³⁹. Although both penicillins appear to be effective in the parenteral regimens used for early and late syphilis, these regimens have not yet been comparatively studied¹⁶. Nor has parenteral procaine penicillin plus oral probenecid been compared with intravenous penicillin in the treatment of neurosyphilis. The optimal treatment schedule for syphilis in pregnant women is not known. The exact value of the serum titre response of cardiolipin/non-treponemal tests has never been fully elucidated; universally accepted standards for cure or failure using the serological response do not exist. The control of syphilis over the past 50 years has been excellent, however, compared to the pre-penicillin age. Late complications of syphilis and/or failures of treatment are uncommon, even in patients with concomitant HIV infection, indicating that the treatment schedules presently used seem fairly adequate, although there remains a need for properly controlled studies
- The risk of a syphilis patient with a concomitant HIV infection of developing a more aggressive course with (early) neurosyphilis, ocular syphilis, treatment failure and relapse appears to be slightly increased^{1,14,16,40}. Consequences thereof: (a) HIV-antibody test should always be offered to patients with syphilis of any stage not yet adequately treated, as the HIV-status may affect the policy for diagnosis, follow-up and rarely of treatment; (b) careful follow-up of syphilis patients with concomitant HIV-infection, including CSF examination 2 years after treatment of early syphilis and at the initial diagnostic stage of an HIV-infected patient with late latent syphilis or latent syphilis of unknown duration
- The Russian Federation has devised regularly updated treatment recommendations, lastly from 1999 (see Appendix). These carefully worked-out recommendations often differ from those issued in other European countries and the USA. The vast experience in the Russian Federation does therefore not provide other countries with answers, due to differences of dosage and duration of commonly used antibiotics.

Early syphilis (primary, secondary and early latent acquired <1 year previously), recommended regimen^{1,14,16,41–45}

First-line therapy options:

- Benzathine penicillin (Penidural®) 2.4 million units intramuscularly (IM) (each buttock 1.2 million units) on day 1^{1,5,41,42,44,45}. Using lidocaine solution as part of the solvent reduces the discomfort associated with injection
- Procaine penicillin 600 000 units IM daily for 10–14 days^{5,41,42,46}. If unable to give daily procaine penicillin on the weekend, one may give long-acting Biclinocillin (benethamine penicillin 1 million units) 1.67 million units IM on Friday to cover the weekend⁴². Some physicians recommend a larger dose of procaine penicillin (1.2 million units)⁴¹, certainly for heavier patients (e.g. 80–100 kg)
- Benzyl penicillin 1 million units IM daily for 10–14 days⁴⁴.

Penicillin allergy or parenteral treatment refused:

- Doxycycline 200 mg daily (either 100 mg twice daily or as a single 200 mg dose) for 14 days^{1,16,20,25}
- Tetracycline 500 mg four times daily for 14 days^{1,16,20}
- Erythromycin 500 mg four times daily for 14 days^{16,20}
- Other options: azithromycin 500 mg once daily for 10 days^{16,26–28}, ceftriaxone 250–500 mg IM once daily for 10 days^{29,30}.

Late latent (acquired ≥ 1 year previously or of unknown duration), cardiovascular and gummatous syphilis, recommended regimen

First-line therapy options:

- Benzathine penicillin (Penidural®) 2.4 million units IM (each buttock 1.2 million units) weekly on day 1, 8 and 15^{1,41,43–45}. Reconstitution of benzathine penicillin with lidocaine reduces the discomfort associated with injection
- Procaine penicillin 600 000 units IM daily for 17–21 days^{41,43}. If unable to give daily procaine penicillin on the weekend, one may give long-acting Biclinocillin (benethamine penicillin 1 million units) 1.67 million units IM on Friday to cover the weekend⁴². Some physicians recommend a larger dose of procaine penicillin (1.2 million units)⁴¹, certainly for heavier patients (e.g. 80–100 kg)
- Benzyl penicillin 1 million units IM daily for 21 days⁴⁴.

Penicillin allergy or parenteral treatment refused:

- Doxycycline 200 mg daily (either 100 mg twice daily or as a single 200 mg dose) for 21–28 days^{1,20,25,41,43–45}

- Tetracycline 500 mg 4 times daily for 28 days¹
- Erythromycin 500 mg 4 times daily 28 days²⁰.

Neurosyphilis and ocular syphilis, recommended regimen

- Biological plausibility suggests that regimens that achieve treponemicidal levels of an antibiotic in CSF should be the treatment of choice. Options are intravenous (IV) or parenteral (IM)/oral therapy using probenecid. Data comparing these two options are lacking
- There are conflicting data over the effectiveness of producing a treponemicidal CSF penicillin level using the procaine penicillin/probenecid combination^{20,47,48}. Concern that the CSF penicillin level is increased at the expense of the central nervous system (CNS) tissue level^{47,49} may not be relevant, because the levels in both CSF and CNS tissue are in fact higher with probenecid than without, with a relatively much higher level in the CSF²⁰. The experience in the UK with treatment of neurosyphilis with the procaine penicillin/probenecid combination has been positive so far. The availability of probenecid may be a problem however
- In ocular syphilis, also in uveitis syphilitica of short duration, effective treatment can be realized with parenteral benzathine penicillin^{50,51}, but in patients with serious ocular involvement (cave: ocular syphilis is often associated with (a)symptomatic neurosyphilis), or ocular involvement of longer duration (with threat of permanent loss of vision), treatment as for neurosyphilis should be preferred.

First-line therapy:

- Benzyl penicillin 12–24 million units IV daily, as 2–4 million units every 4 hours for 10–21 days^{1,41,43,44}
- Benzyl penicillin 0.15 million units/kg/day IV, spread over 6 doses (every 4 hours) for 10–14 days^{45,49}
- Procaine penicillin 1.2–2.4 million units IM daily PLUS probenecid 500 mg orally 4 times daily, both for 10–21 days^{1,41,43}.

Penicillin allergy or parenteral treatment refused:

- Doxycycline 200 mg twice daily for 28–30 days^{25,41,43,45}.

Follow up

Repeat CSF examination should be performed not earlier than 1–2 years after treatment of neurosyphilis, unless clinical deterioration occurs. If performed earlier, e.g. at 3 or 6 months, non-relevant CSF findings suggesting aggravation due to the so-called paradoxical response may cause unnecessary confusion⁵². In meningovascular

neurosyphilis the number of mononuclear cells in CSF generally normalizes faster (within 6–12 months) than in parenchymatous neurosyphilis (within 1–2 years). As has been stated above, the number of mononuclear cells in CSF and the IgM-index should become normal within 1–2 years, while albumin quotient, IgG-index and TPHA-index may remain abnormal and the CSF-VDRL-test positive.

SPECIAL SITUATIONS

Pregnancy

In pregnant women with untreated early syphilis, 70–100% of infants will be infected, with stillbirths in up to one-third of cases. Standard treatment has been used with good results, but because of some reports of insufficient response in mother and infant, more aggressive treatment has been advocated^{1,16,36–38}.

First-line options for treatment of early syphilis (acquired <2 years previously):

- Benzathine penicillin (Penidural®) 2.4 million units IM (each buttock 1.2 million units) weekly on days 1 and 8¹
- Procaine penicillin 600 000 or 1.2 million units IM daily for 10–14 days⁴².

Penicillin allergy:

- Desensitization to penicillin may be considered followed by first-line treatment¹
- Alternative options:
 - Azithromycin, 500 mg once daily for 10 days, which has been used for chlamydial infection in pregnant women as reported in a Cochrane analysis⁵³. Published evidence of safety of use during pregnancy is limited however
 - Ceftriaxone, 250–500 mg IM daily for 10 days, may also be given during pregnancy⁵⁴. Published evidence of safety of use during pregnancy is limited however
 - Consideration might be given on re-treating mothers with doxycycline after delivery.

Prevention of congenital syphilis by serological screening during pregnancy and preventive neonatal treatment:

- Serological screening is recommended in the USA at: (a) initial pregnancy control; (b) 28 weeks of gestation; (c) delivery, if high-risk for congenital syphilis¹. In The Russian Federation it is recommended at: (a) initial pregnancy control; (b) 21 weeks of gestation; (c) 36 weeks of gestation. Each country should decide on its own screening policy, if possible based on a cost-effectiveness analysis

- All infants born to sero-positive mothers should be treated with a single dose of benzathine penicillin 50 000 units/kg IM, whether or not the mother was treated during pregnancy, especially in high-prevalence countries^{1,41}.

Congenital syphilis

Diagnosis

Confirmed congenital infection:

- *T. pallidum* demonstrated by dark-field microscopy, immunofluorescent microscopy, PCR or specific staining of specimens for histopathological examination, e.g. from skin lesions, navel, placenta or autopsy material¹⁴.

Presumed congenital infection^{1,42,55}:

- A stillborn neonate with a positive treponemal test for syphilis
- Children with a positive treponemal test for syphilis in combination with one of the following:
 - Persistent rhinitis, condylomata lata, osteitis, periostitis, osteochondritis, ascites, cutaneous and mucous membrane lesions, hepatitis, hepatosplenomegaly, glomerulonephritis, haemolytic anaemia
 - Radiological abnormalities of the long bones suggestive of congenital syphilis
 - A positive VDRL test in CSF
 - A 4-fold increase or more of the TPHA/MHA-TP titre in the child's as opposed to the mother's serum (both obtained simultaneously at birth)
 - A 4-fold increase or more of the titre of a cardiolipin/non-treponemal test in the child's as opposed to the mother's serum (both obtained simultaneously at birth)
 - A 4-fold increase or more of the titre of a cardiolipin/non-treponemal test within 3 months after birth
 - A positive 19S-IgM-FTA-abs test, EIA-IgM and/or IgM-immunoblot for *T. pallidum* in the child's serum
 - A mother, in whom syphilis was confirmed during pregnancy, but who was not adequately treated either before or during pregnancy
- A child >12 months-of-age with a positive treponemal serological test for syphilis.

Late congenital syphilis including stigmata:

- Interstitial keratitis, Clutton's joints, Hutchinson's incisors, mulberry molars, high palatal arch, rhagades, deafness, frontal bossing, short maxilla, protuberance of mandible, saddlenose deformity, sterno-clavicular thickening, paroxysmal cold haemoglobinuria, neurological or gummatous involvement

- Serological tests can be negative in infants infected in late pregnancy and should be repeated. When the mother is treated during the last trimester of pregnancy, the treatment can be inadequate for the child and the child may still develop congenital syphilis.

Investigations

- VDRL, TPHA/MHA-TP (quantitative), anti-treponemal IgM (19S-IgM-FTA-abs test and/or IgM-immunoblot or EIA-IgM) from infant's blood and not umbilical cord blood, because false-positive and -negative tests may result⁵⁵
- Blood: full blood count, liver function, electrolytes, albumin, IgG, IgM
- CSF: cells, albumin, IgG, IgM, TPHA, VDRL
- X-rays of long bones
- Ophthalmic assessment as indicated.

Treatment options

- Benzyl penicillin 150 000 units/kg IV daily (administered in 6 doses every 4 hours) for 10–14 days^{1,41,44}
- Procaine penicillin 50 000 units/kg IM daily for 10–14 days^{1,41,42}
- If CSF is normal: benzathine penicillin 50 000 units/kg IM (single dose)^{1,41}.

HIV-infected patients

General remarks

- Serological tests for syphilis in patients with HIV co-infection are generally reliable for the diagnosis of syphilis and for evaluation of treatment response
- False-negative and -positive tests and delayed appearance of seroreactivity have been reported^{1,14,16}
- In HIV-infected individuals with clinical suspicion of syphilis and (repeatedly) negative syphilis serology, it is advisable to perform other diagnostic tests apart from the preliminary screening test, e.g. histological, immunofluorescent or PCR examination of a biopsy from a clinically suspected lesion and direct dark-field microscopy of the exudate of early syphilitic lesions for spirochaetes
- HIV-infected patients with early syphilis appear to have a slightly increased risk of (early) neurological and ocular involvement and higher rate of treatment failure with benzathine penicillin including more frequent serological relapse^{1,14,16,40}. Therefore careful follow-up is essential
- CSF examination is advisable^{1,14,16}:
 - As part of the initial diagnostic programme in HIV-infected patients with late latent syphilis or latent syphilis of unknown duration (see earlier in the text)
 - 2 years after treatment of early syphilis (not advised for non-HIV infected patients).

Treatment of syphilis in patients with concomitant HIV infection

- Treatment should be given as for non-HIV-infected patients.

Note (1): Careful follow-up is essential (see above and at follow-up).

Note (2): In the UK, where neurosyphilis is often treated with procaine penicillin IM plus probenecid orally, which regimen can be given on an out-patient basis, it has been suggested that HIV-infected syphilis patients should be treated with the procaine regimen mentioned, to prevent the development of neurological involvement. Hard evidence for this policy is lacking, however^{42,43}.

Reactions to treatment

Patients should be warned of possible reactions to treatment. Facilities for resuscitation should be available in the treatment area.

Jarisch–Herxheimer reaction

- An acute febrile illness with headache, myalgia, chills and rigors, resolving within 24 hours
- Common in early syphilis, but is usually not important unless there is neurological or ophthalmic involvement or in pregnancy, when it may cause fetal distress and premature labour
- Uncommon in late syphilis, but can potentially be life-threatening if involvement of strategic sites (e.g. coronary ostia, larynx, nervous system)
- Prednisolone can abolish the febrile episode⁵⁶, but is unproven in ameliorating local inflammation. Nevertheless, severe clinical deterioration in early syphilis with optic neuritis and uveitis has been reported following treatment. As a steroid is also used in the management *per se*, biological plausibility would suggest that it may help
- Systemic treatment with a blocker of tumour necrosis factor (TNF) may be more effective than systemic treatment with a corticosteroid⁵⁷
- Management:
 - If cardiovascular or neurological involvement (including optic neuritis) exists, in-patient management is advisable
 - Prednisolone 10–20 mg 3 times daily for 3 days, starting anti-treponemal treatment after 24 hours of commencing prednisolone
 - Antipyretics.

Procaine reaction (procaine psychosis, procaine mania, Hoigné syndrome)

- Due to inadvertent intravenous injection of procaine penicillin; may be minimized by the 'aspiration technique' of injection

- Characterized by fear of impending death, may cause hallucinations or fits immediately after injection. Lasts less than 20 minutes
- Management:
 - Exclude anaphylaxis
 - Calm and verbal reassurance: restraint may be necessary
 - Diazepam rectally/IV/IM if convulsions.

Anaphylactic shock

- Facilities for treatment of anaphylaxis should be available as penicillin is one of the commonest causes
- Management:
 - Epinephrine (adrenaline) 1:1000 IM 0.5 ml, followed by:
 - IM/IV antihistamine, e.g. chlorpheniramine 10 mg
 - IM/IV hydrocortisone 100 mg.

MANAGEMENT OF PARTNERS

- All patients with syphilis should be seen for partner notification (notification by the patient = patient referral, by a health department = provider referral), health education, STD prevention and confirmation of any past treatment history
- Although the division of latent syphilis in early and late stages has been useful for treatment and partner notification, this classification can be problematic for use in surveillance, as a substantial number of late, hypothetically non-infectious, latent syphilis cases (latent syphilis of unknown duration was classified as late latent) turned out to be probable early, infectious, latent syphilis according to one report¹⁴
- Secondary syphilis relapse can occur within the first 2 years of infection, and syphilis is thought to be infectious through intercourse for up to 2 years after acquisition
- Partner notification assists community efforts to reduce the disease burden, fulfils ethical obligations to warn the unsuspecting and, probably not unimportant, can delineate the risk networks hosting transmission. Partner notification programmes may have poor results though, which poses a problem because syphilis may cause serious morbidity¹⁴
- For patients with primary syphilis, sexual partners within the past 3 months should be notified as the incubation period is up to 90 days. Partner notification may have to extend to 2 years for patients in secondary syphilis with clinical relapse or in early latent syphilis
- 46–60% of contactable sexual partners, including pregnant women, of patients with early syphilis are likely to be infected

- Immediate epidemiological treatment for sexual partners should be considered (especially of pregnant partners), unless partners are able to attend regularly for exclusion of syphilis through clinical and serological examination
- Serological tests for syphilis should be performed at the first visit and repeated at 6 weeks and 3 months
- Notification of syphilis to the relevant authority is required in many European countries, particularly early syphilis and congenital syphilis.

FOLLOW UP

The follow up to ascertain cure and detect reinfection or relapse is achieved by assessing the clinical and serological response.

- For early syphilis, minimum clinical and serological (cardiolipin/non-treponemal tests: VDRL or RPR) assessment according to the following follow-up scheme might be used: monthly during the first 3 months after treatment, then at 6 and 12 months. Follow-up of HIV-infected patients treated for early syphilis should be more frequent, e.g. at 1, 2, 3, 6, 9, 12, 18 and 24 months^{1,42}, and may be ended by CSF examination¹⁴
 - After treatment of early syphilis the titre of cardiolipin/non-treponemal tests (e.g. VDRL and/or RPR) should decline by 2 dilution steps (4-fold) within 6 months (within 1 year for HIV-positive patients)¹.
 - If this does not occur, should additional treatment be given (according to the CDC¹: benzathine penicillin 2.4 million units IM on day 1, 8 and 15)? If the clinical response has been adequate, one might decide against additional treatment. If the clinical response was inadequate or impossible to monitor as in latent syphilis, one might decide in favour of additional treatment
- In late (latent) syphilis the serological response of cardiolipin/non-treponemal tests is often absent. In non-HIV-infected late latent syphilis patients with a reactive cardiolipin/non-treponemal test, which remains stable in the lowest titre range, follow-up after treatment is generally not indicated
- Early clinical relapse tends to occur in the oral and anal regions
- An increase of >2 dilution steps (4-fold) in a cardiolipin/non-treponemal test suggests reinfection or reactivation
- Follow-up examination of CSF should be performed 1–2 years after treatment of neurosyphilis
- Specific treponemal tests may remain positive for life following effective treatment; proper documentation is necessary to prevent unnecessary re-treatment

- Reinfection or relapse should be re-treated preferably with supervised treatment schedules to ensure compliance, and sexual partners should be rescreened.

APPENDIX

Syphilis treatment recommendations for the Russian Federation, formulated by the Central Research Institute for Skin and Venereal Disease, Moscow, approved by the Ministry of Health

Introduction

The management of syphilis in the former USSR was always strictly regulated. The first regulations were published in the USSR in 1948. Those regulations concerned both diagnosis and treatment of the disease. Since 1948 the regulations have been updated several times. The epidemic of syphilis that occurred in the Russian Federation during the last decade necessitated a change in the management of syphilis. Here, the last treatment regulations of 1999 are given.

Principles of syphilis management

- 1 Specific treatment: symptoms suggestive of syphilis, confirmed by positive laboratory tests
- 2 Preventive treatment: absence of clinical and laboratory abnormalities, but a history of sexual or other close physical contacts <2 months previously with a patient, then suffering from an early form of syphilis
- 3 Prophylactic treatment:
 - (a) of a pregnant woman, who was treated for syphilis in the past, but still has positive serologic tests
 - (b) of a pregnant woman, who acquired syphilis during that pregnancy
 - (c) of a newborn, from a woman who acquired syphilis during the pregnancy
- 4 Treatment *ex juvantibus*: no evident laboratory abnormalities, but patients have lesions in internal organs suspected to be due to syphilis
- 5 Syndromic treatment: clinical symptoms suggestive of syphilis without opportunity to perform confirmatory laboratory tests.

Serologic tests

Part of a separate statutory protocol, formulated by the Central Research Institute for Skin and Venereal Diseases, Moscow, approved and issued as a law early in 2001 by the Ministry of Health.

Primary screening tests (in 2001 the TPHA has been introduced as a primary screening test for a validation period of 2 years; in blood donors that test was already routinely used):

- Reaction of microprecipitation (RMP, i.e. VDRL test or rapid plasma reagin (RPR) test) or
- Complex of serologic reactions (CSR) or TPHA or EIA.

Confirmation tests:

- TPHA or EIA or FTA-abs test or TPI

Complex of serologic reactions (CSR):

- Reaction of microprecipitation (RMP, i.e. VDRL test or RPR)
- and
- Two complement-fixation reaction (CFR) tests using reaction of Wassermann (RW) with a cardiolipin and a treponemal antigen.

Follow-up tests (parameter of serologic response):

- RMP or CSR

Antibiotics (in alphabetical order) recommended for treatment of syphilis

- 1 Azithromycin
- 2 Ampicillin
- 3 Benzathine benzylpenicillin (dibenzylethylenediamine salt of penicillin, BBP) (Bicillin-1, Retarpen[®], Extencillin[®])
- 4 Bicillin-3 (combination of dibenzylethylenediamine, novocaine and sodium salts of penicillin in a rate of 1:1:1)
- 5 Bicillin-5 (combination of dibenzylethylenediamine and novocaine salts in a rate of 4:1)
- 6 Benzylpenicillin sodium salt (SBP)
- 7 Benzylpenicillin novocaine salt (NBP)
- 8 Ceftriaxone
- 9 Doxycycline
- 10 Erythromycin
- 11 Oxacillin
- 12 Procaine benzylpenicillin (PBP)
- 13 Tetracycline.

Preventive treatment

- 1 BBP (Extencillin[®], Retarpen[®], Bicillin-1) 2.4 million units IM once, Bicillin-3 1.8 million units or Bicillin-5 1.5 million units IM twice (within one week)
- 2 PBP 1.2 million units IM once daily or NBP 600 000 units IM twice daily for 7 days
- 3 In patients, who received seropositive blood from a donor: treatment as in primary syphilis if transfusion <3 months previously or serologic tests if transfusion ≥3 months previously.

If contact with a syphilis patient was >2 months previously, serologic tests (CSR plus FTA-abs test) should be performed twice within a period of 2 months, if contact was >4 months previously, serologic tests (CSR plus FTA-abs test) should be performed once.

Management of primary syphilis

- 1 BBP (Extencillin[®], Retarpen[®]) 2.4 million units IM twice with 7 days' interval (day 1 and 8) or Bicillin-1 2.4 million units IM thrice with 5 days' interval (day 1, 6 and 11)
- 2 Bicillin-3 1.8 million units IM or Bicillin-5 1.5 million units IM for a total of 5 doses given twice a week

- 3 PBP 1.2 million units IM daily for 10 days or NBP 600 000 units IM twice daily for 10 days
- 4 SBP 1 million IM 4 times daily (every 6 hours) for 10 days.

Management of secondary and early latent syphilis (<2 years previously acquired)

- 1 BBP (Extencillin[®], Retarpen[®]) 2.4 million units IM thrice with 7 days' interval (day 1, 8 and 15) or Bicillin-1 2.4 million units IM 6 times with 5 days' interval (day 1, 6, 11, 16, 21 and 26)
- 2 Bicillin-3 1.8 million units IM or Bicillin-5 1.5 million units IM for a total of 10 doses given twice a week
- 3 PBP 1.2 million units IM daily for 10 days or NBP 600 000 units IM twice daily for 20 days
- 4 SBP 1 million units IM 4 times daily (every 6 hours) for 20 days.

The last two regimens (3 and 4) are recommended in early latent syphilis >6 months previously acquired and in secondary syphilis with leukoderma or alopecia.

Management of early visceral syphilis or early neurosyphilis

Definition of early visceral syphilis: specific involvement of internal organs during the early stage of syphilis (<2 years previously acquired).

Definition of early neurosyphilis: specific involvement of the central nervous system (meningovascular syphilis) in the first 3 years after infection. **Note:** These patients must be treated as in-patients under the supervision of a physician.

(A) Therapy of early visceral syphilis:

- 1 SBP 1 million units IM four times daily for 20 days
- 2 NBP 600 000 units IM twice daily or PBP 1.2 million units IM once daily for 20 days

In all cases additional symptomatic therapy is recommended (e.g. systemic corticosteroids).

(B) Therapy of early neurosyphilis:

- 1 SBP 10 million units IV in 400 ml of isotonic solution twice daily during 1.5–2 hours of infusion for 14 days
- 2 SPB 2–4 million units IV 6 times daily for 14 days.

Management of tertiary and late latent syphilis (≥2 years previously acquired)

Definition of tertiary syphilis: gummatous and/or tubercular cutaneous lesions with or without (cardiovascular and/or gummatous) visceral involvement.

In tertiary syphilis with cutaneous lesions with concomitant specific involvement of internal organs the recommended regimens are the same as in late visceral syphilis.

In tertiary syphilis with cutaneous lesions without visceral involvement and late latent syphilis the following regimens are recommended:

- 1 SBP 1 million units IM 4 times daily for 28 days, followed by the same course for 14 days after 2 weeks' interval
- 2 NBP 600 000 units IM twice daily for 28 days, followed by the same course for 14 days after 2 weeks' interval
- 3 PBP 1.2 million units IM once daily for 20 days, followed by the same course for 10 days after 2 weeks' interval.

Note on the use of PBP: a course of 28 days is recommended, as in late visceral syphilis, unless adverse reactions prevent prolongation of the course.

Management of late visceral syphilis and late neurosyphilis

Definition of late visceral syphilis: cardiovascular syphilis and/or gummatous involvement of internal organs.

Definition of late neurosyphilis: specific parenchymatous involvement of the central nervous system, i.e. tabes dorsalis, dementia paralytica, taboparalysis, primary atrophy of the optical nerve.

(A) Late visceral syphilis:

- 1 SBP 400 000 units IM 8 times daily for 28 days, followed by a second course for 14 days after 2 weeks' interval
- 2 NBP 600 000 units IM twice daily or PBP 1.2 million units IM once daily for 28 days, followed by a second course for 14 days after 2 weeks' interval.

Treatment should be initiated, before the first penicillin course, by 2 weeks of an oral broad spectrum antibiotic (tetracycline or erythromycin 4 × 500 mg a day).

(B) Late neurosyphilis: the recommended regimens are the same as in early neurosyphilis, but with an additional second course after 2 weeks interval.

Penicillin allergy: alternative regimens for the management of syphilis

- 1 Doxycycline 2 × 100 mg or tetracycline 4 × 500 mg orally for 10, 15 or 30 days (for preventive treatment, treatment of primary and secondary syphilis and treatment of early latent syphilis respectively)
- 2 Semisynthetic penicillines: oxacillin or ampicillin 1 g IM 4 times daily for 10, 14 or 28 days (for preventive treatment, treatment of primary or secondary syphilis and treatment of early latent syphilis respectively)
- 3 Ceftriaxone 250 mg IM once daily for 5 or 10 days (for preventive treatment and treatment of primary syphilis respectively), 500 mg IM once daily for 10 days (secondary and early latent

- syphilis) or 1000–2000 mg IM once daily for 14 days (late latent and neurosyphilis).
- 4 Azithromycin 500 mg orally once daily for 10 days for early syphilis (primary, secondary and early latent syphilis).

Specific and prophylactic treatment in pregnancy

Specific treatment:

- (A) Specific treatment of pregnant women before the 18th week of pregnancy is the same as in non-pregnant women
- (B) For specific treatment after the 18th week of pregnancy the following regimens are recommended:
- Primary syphilis:
 - 1 PBP 1.2 million units IM daily or NBP 600 000 units IM twice daily for 10 days
 - 2 SBP 1 million units IM 4 times daily (every 6 hours) for 10 days
 - Secondary and early latent syphilis:
 - 1 The same regimens as in primary syphilis, but for 20 days.

Prophylactic treatment of pregnant women, who have been treated for syphilis in the past, but are still seropositive:

- (A) Treatment, the same regimen as for primary syphilis, is usually started after the 20th week of pregnancy.
- (B) If specific treatment is given after the 18th week, that treatment should be followed by prophylactic treatment.

Alternative therapy in case of penicillin allergy: erythromycin or semisynthetic penicillins.

Management of syphilis in children

Prophylactic treatment of a newborn is indicated if the mother, seropositive at the time of labour, of a clinically asymptomatic newborn was not treated or treated too late (after the 32nd week of pregnancy):

- (A) If the mother was not treated, the prophylactic regimen for the newborn is the same as in congenital syphilis
- (B) If the mother was insufficiently treated or if she was still seropositive at labour after adequate treatment, the following regimens are recommended:
- 1 SBP 100 000 units/kg/day IM 6 times daily for 10 days
 - 2 NBP 50 000 units/kg/day IM twice daily or PBP 50 000 units/kg/day IM once daily for 10 days
 - 3 BBP 50 000 units/kg twice with 7 days interval (day 1 and 8).

Specific treatment of a newborn with early congenital syphilis, symptomatic or asymptomatic:

- (A) Newborn with normal CSF:
- 1 SBP 100 000 units/kg/day IM 6 times daily for 14 days
 - 2 NBP 50 000 units/kg/day IM twice daily or PBP 50 000 units/kg/day IM once daily for 14 days
 - 3 BBP 50 000 units/kg/day thrice with 7 days interval (day 1, 8 and 15), provided the newborn is not <2 kg in weight
- (B) Newborn with abnormal CSF or CSF not investigated:
- 1 The same regimens as for (A), but BBP is not recommended

Penicillin allergy, alternative treatment:

- 1 Oxacillin or ampicillin or ceftriaxone (80 mg/kg/day for 14 days).

Specific treatment of late congenital syphilis:

- 1 PBP 50 000 units/kg/day IM once daily or NBP 50 000 units/kg/day IM twice daily for 28 days, followed by a second course for 14 days after 2 weeks' interval
- 2 SBP 50 000 units/kg/day IM 6 times daily for 28 days, followed by a second course for 14 days after 2 weeks' interval.

Clinico-serological follow up after treatment of syphilis

Follow up:

- After preventive treatment of adults and children and after treatment of primary syphilis: at 3 months
- After treatment of early forms of syphilis in patients with a positive CSR (RMP): until complete negatvation and for 6 months thereafter
- After treatment of late forms of syphilis and after treatment of neurosyphilis: during 3 years (serum CSR every 6 months during 2nd and 3rd year after treatment, specific seroreactions once a year); after treatment of neurosyphilis: examination of CSF every 6 months during 3 years
- Seroresistant patients are followed during 3 years
- Newborns free from congenital syphilis, but born from mothers with syphilis, are followed during 1 year irrespective of prophylactic treatment.

Seroresistance and additional treatment:

- Seroresistance is defined as a persistently positive CSR >1 year after adequate specific treatment of early syphilis
- Delayed return to negative serology: decline in titre of reagins, at least 4-fold (2 steps), ≥ 1 year after adequate specific treatment
- In such cases the following additional treatment regimens are recommended:
 - 1 SBP 1 million units IM 6 times daily for 20 days
 - 2 PBP 1.2 million units IM once daily or NBP 600 000 units IM twice daily for 20 days

- 3 BBP 2.4 million units IM thrice with 7 days' interval (day 1, 8 and 15)
- 4 Ceftriaxone 1000 mg IM daily for 10 days.

Prerequisites for cure:

- Administration of adequate treatment
- Normalization of clinical symptoms
- Normalization of serologic reaginic reactions and other relevant laboratory tests.

Removal of a patient from the register requires:

- Final complete serologic testing including, after neurosyphilis, CSF examination
- Specialist examination of organs previously involved with late syphilis, including (early) visceral syphilis and neurosyphilis.

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MANAGEMENT OF SPECIFIC INFECTIONS

European guideline for the management of gonorrhoea

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INTRODUCTION

Infection with *Neisseria gonorrhoeae* predominantly involves the epithelial lining of the urethra, endocervix, rectum, pharynx and conjunctiva. Transluminal spread of infection may occur to involve the epididymis and prostate in men and the endometrium and pelvic organs in women. Haematogenous dissemination may also occur from infected mucous membranes, but is uncommon.

DIAGNOSIS

Clinical

Men

- Symptoms and signs of urethritis, characterized by urethral discharge and burning on micturition
- Rectal infection may cause anal discharge or perianal pain
- Acute epididymo-orchitis usually in men aged <40 years
- Asymptomatic infection can occur: urethra <10%, rectum >85%, pharynx >90%
- Disseminated infection causing fever, petechial or pustular skin lesions, asymmetrical arthralgia, septic arthritis, tenosynovitis. Very rarely meningitis or endocarditis.

Women

- Altered vaginal discharge and signs of cervicitis (mucopurulent endocervical discharge, contact bleeding)
- Acute lower abdominal pain and tenderness
- Asymptomatic infection is common: uterine cervix >50%, rectum >85%, pharynx >90%
- Disseminated infection causing fever, petechial or pustular skin lesions, asymmetrical arthralgia, septic arthritis, tenosynovitis. Very rarely meningitis or endocarditis
- Purulent conjunctivitis in neonate.

Indications for testing¹

- Symptoms or signs of urethral discharge
- Mucopurulent cervicitis

- Sexual partner of person with sexually transmitted infection (STI) or pelvic inflammatory disease (PID)
- STI screening at patient request or recent new sexual partner
- Vaginal discharge with risk factor for STI (age <25, recent new sexual partner)
- Acute epididymo-orchitis in male aged <40
- Acute PID
- Purulent conjunctivitis in neonate.

Laboratory

- The diagnosis is established by identification of *N. gonorrhoeae* in genital, rectal, pharyngeal or ocular secretions
- Rapid diagnostic tests (Gram stain/methylene blue stain) by microscopy of urethral, cervical and rectal exudates facilitate an immediate provisional diagnosis in most symptomatic cases by visualization of diplococci in leucocytes
- Culture, amplified antigen detection tests or nucleic acid amplification tests should be performed on all samples. They offer high sensitivity and provide confirmation of the diagnosis. Culture allows sensitivity testing. In asymptomatic patients nucleic acid amplification tests may be more sensitive than culture².

MANAGEMENT

General

The resistance of *N. gonorrhoeae* to antimicrobials is continuing to evolve, notably to penicillin, tetracyclines and quinolones. There are marked geographical variations in resistance and therapy should be informed by local surveillance of sensitivity³. Infection acquired outside Northern Europe should be anticipated to be penicillin-resistant and infection acquired in South East Asia should be anticipated to be both penicillin- and quinolone-resistant.

Indications for therapy

- Identification of intracellular Gram-negative diplococci at a genital site by microscopy
- Positive culture or amplified antigen test from any site for *N. gonorrhoeae*

- On epidemiological grounds, if a recent partner has confirmed gonococcal infection
- On demonstration of a purulent urethral discharge in men or mucopurulent cervicitis in women when rapid diagnostic tests are not available and after specimen collection for laboratory testing. In this circumstance, combined treatment for gonococcal and chlamydial infection should be given.

Recommended regimens for infections of the urethra, cervix and rectum⁴⁻⁷

- Ceftriaxone 250 mg intramuscularly (IM) as single dose, or
- Ciprofloxacin 500 mg oral as single dose, or
- Ofloxacin 400 mg oral as single dose, or
- Cefixime 400 mg oral as single dose, or
- Spectinomycin 2 g IM as single dose
- Co-infection with *Chlamydia trachomatis* is common in patients with gonorrhoea. Treatment for gonorrhoea should routinely be followed with effective treatment for chlamydial infection or sensitive testing to exclude co-infection.

Alternative regimens

- Penicillin regimens (e.g. amoxicillin 2 g or 3 g orally plus probenecid 1 g orally as a single dose) are still appropriate when the isolate is known to be penicillin-sensitive or where the prevalence of penicillin-resistance is known to be <5% and follow-up assessment is routinely performed
- Penicillin therapy that combines a β -lactamase inhibitor (e.g. sultamicillin 2.25 g plus probenecid 1 g as a single oral dose; or amoxicillin 3 g plus clavulanic acid 250 mg plus probenecid 1 g as a single oral dose) may be an appropriate alternative where local efficacy is established
- Other single-dose cephalosporin regimens are highly effective against gonococcal infection, but with less clinical trial data.

Special situations

*Pregnancy/breastfeeding*⁸

Recommended treatments:

- Ceftriaxone 250 mg IM as single dose, or
- Spectinomycin 2 g IM as single dose, or
- Amoxicillin 2 g or 3 g orally plus probenecid 1 g orally as a single dose when *N. gonorrhoeae* isolate is known to be penicillin-sensitive.

Pregnant and breastfeeding women should not be treated with quinolone or tetracycline antimicrobials.

*Pharyngeal gonorrhoea*⁹

Recommended treatments:

- Ceftriaxone 250 mg IM as single dose, or

- Ciprofloxacin 500 mg orally as single dose, or
- Ofloxacin 400 mg orally as single dose.

Single-dose treatments with penicillin or spectinomycin have poor efficacy at eradicating pharyngeal gonorrhoea.

β -lactam allergy

Recommended treatments:

- Ciprofloxacin 500 mg orally as single dose, or
- Spectinomycin 2 g IM as single dose.

Gonococcal epididymitis

Please refer to European guideline on epididymo-orchitis p. 88.

Disseminated gonococcal infection^{4,10}

Recommended management based on expert opinion and accumulated clinical experience.

Initial therapy:

- Ceftriaxone 1 g IM or intravenously (IV) every 24 hours, or
- Cefotaxime 1 g IV every 8 hours, or
- Ciprofloxacin 500 mg IV every 12 hours, or
- Spectinomycin 2 g IM every 12 hours.

Therapy should continue for 7 days, but may be switched 24–48 hours after symptoms improve to one of the following oral regimens:

- Ciprofloxacin 500 mg twice daily, or
- Ofloxacin 400 mg twice daily, or
- Cefixime 400 mg twice daily.

*Ophthalmia neonatorum*¹⁰

- Ceftriaxone 25–50 mg/kg IV or IM as single dose not to exceed 125 mg, or
- Cefotaxime 100 mg/kg IM as a single dose, and
- Frequent conjunctival irrigation with saline.

MANAGEMENT OF PARTNERS

Sexual partners should be treated for gonorrhoea and chlamydial infection, preferably after evaluation for sexually acquired infection. The following partners should be included: in symptomatic cases of gonorrhoea, all sex partners within the preceding 14 days or last partner if longer; in asymptomatic cases all partners within the preceding 90 days.

Recommended treatments for partners:

- Ceftriaxone 250 mg IM as single dose, or
- Ciprofloxacin 500 mg oral as single dose, or
- Ofloxacin 400 mg oral as single dose, or
- Cefixime 400 mg oral as single dose, or
- Spectinomycin 2 g IM as single dose, or
- Amoxicillin 3 g plus probenecid 1 g orally as a single dose when source *N. gonorrhoeae* is known to be penicillin-sensitive.

FOLLOW UP AND TEST OF CURE

At least one follow-up evaluation is recommended to confirm compliance with therapy, resolution of symptoms and signs, and partner notification.

Test of cure is not routinely necessary if antibiotic sensitivity testing is available. Indications for test of cure include:

- Persistence of symptoms
- Re-exposure to infection
- Possible resistance to therapy given
- Reassurance of the patient (psychological)
- Non-adherence
- When stipulated by national or local practice.

Notification

- Infections with *N. gonorrhoeae* should be notified to local, regional and national authorities as required by statute.

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MANAGEMENT OF SPECIFIC INFECTIONS

European guideline for the management of chlamydial infection

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UROGENITAL INFECTIONS AMONG ADULTS

Urogenital infection with pathogen *Chlamydia trachomatis* (serotypes D–K) is the most common bacterial sexually transmitted infection in both men and women in European countries. Asymptomatic infection is common especially in women (up to 80%) and often unrecognized, leading to infection in sexual partners and to long-term sequelae. Contact tracing is of great importance for the diagnosis and treatment of asymptomatic infected persons.

Clinical diagnosis

Signs and symptoms are mainly due to cervicitis and urethritis and to complications.

Women

Urogenital infection is symptomatic in approximately 30% of cases:

- Mucopurulent cervicitis
- Purulent vaginal discharge
- Lower abdominal pain
- Postcoital or intermenstrual bleeding
- Dysuria
- Signs of pelvic inflammatory disease (PID), chronic pelvic pain.

Men

Urogenital infection is symptomatic in approximately 75% of cases:

- Urethral discharge
- Dysuria
- Signs of epididymitis and prostatitis.

Both

Symptoms common to men and women include:

- Anorectal discharge or discomfort
- Conjunctivitis
- Arthralgia.

Laboratory diagnosis

Chlamydial diagnosis has rapidly developed during the last few years. The ideal diagnostic test will have a sensitivity greater than 90% and a specificity greater than 99%. Nucleic acid amplification

(NAA) assays approach most closely these demands. However, the test utilized should correspond to the available healthcare resources, which differ in European countries¹. For screening programmes, techniques which are suitable for non-invasive samples (urine, introital) are preferred.

Cell culture

- Sensitivity range: 40–85% when using genital specimens (cervical, urethral)
- Advantages: highly specific, still essential for medicolegal diagnosis
- Disadvantages: needs expertise, only appropriate for a small number of invasive samples (cervical, urethral).

Direct fluorescent antibody assays (DFA)

- Sensitivity range: 50–90%, dependent on expertise and number of elementary bodies in the specimen
- Advantages: suitable for invasive and non-invasive samples (e.g. urine)
- Disadvantages: unsuitable for large numbers of specimens, time-consuming.

Enzyme immunoassays

- Sensitivity range: 20–85% dependent on the kind of assay
- Advantages: the testing of large numbers of samples is practicable, rapid and automatable, low price
- Disadvantages: high specificity only if positive results are confirmed, suitable only for invasive (cervical, urethral) samples.

RNA-DNA hybridization

- Sensitivity range: 70–85%
- Advantages: rapid and automatable, the testing of large numbers of samples is practicable, the concomitant diagnosis of gonococcal infection is possible
- Disadvantage: suitable only for invasive (cervical, urethral) samples.

Nucleic acid amplification (NAA)

- Sensitivity range: 70–95%
- Advantages: high specificity (97–99%), the testing of large numbers of samples is practicable, invasive (cervical, urethral) and non-invasive (urine and vulvovaginal) samples

can be used^{2,3}, the concomitant diagnosis of gonococcal infection is possible with some assays

- Disadvantages: expensive, particular care is required to prevent contamination in laboratories, inhibitors may be a problem, especially for urine samples.

Sampling

Women

Invasive swabs (cervical and urethral) if non-NAA assays are used, invasive and non-invasive samples (first void urine and introital swabs) if NAA assays are used³.

Men

Urethral swabs if non-NAA assays are used, invasive and non-invasive samples (first void urine) if NAA assays are used.

Indications for testing

- Symptoms due to lower genital tract infection caused by *C. trachomatis*
- Conjunctivitis caused by *C. trachomatis*⁴
- Complications (PID, sexually acquired reactive arthritis, chronic-pelvic pain, tubal infertility, epididymo-orchitis, adult conjunctivitis), which may be caused by *C. trachomatis*
- Contact tracing/partner notification
- Screening of young adult women <25 years-of-age
- Screening of individuals with new or multiple partners who report non-use or inconsistent use of barrier contraception
- Screening of women during pregnancy
- Exclusion of infection before medical intervention (termination of pregnancy, IUD insertion, artificial insemination).

Indications for treatment

- Confirmed oculogenital *C. trachomatis* infection
- Infection with *C. trachomatis* in the partner (see 'Management of partners')
- If laboratory tests for *C. trachomatis* are not available in a patient with a confirmed *Neisseria gonorrhoeae* infection
- If laboratory tests for *C. trachomatis* are not available in a patient with clinical signs of a chlamydial infection.

Treatment of adults, adolescents, children >45 kg

Recommended regimens^{5,6}

- Azithromycin 1 g orally, single dose, or
- Doxycycline 100 mg orally twice a day for 7 days.

Alternative regimens (equivalent)

- Erythromycin base 500 mg orally 4 times a day for 7 days, or

- Ofloxacin 200 mg orally twice a day for 7 days, or
- Roxithromycin 150 mg orally twice a day for 7 days, or
- Clarithromycin 250 mg orally twice a day for 7 days.

Treatment of pregnant women

Recommended regimens

- Erythromycin base 500 mg orally 4 times daily for 7 days, or
- Amoxicillin 500 mg orally 3 times daily for 7 days, or
- Josamycin 750 mg orally twice daily for 7 days.

Alternative regimens

- Erythromycin base 250 mg orally 4 times daily for 14 days, or
- Erythromycin ethylsuccinate 800 mg orally 4 times daily for 7 days, or
- Erythromycin ethylsuccinate 400 mg orally 4 times daily for 14 days, or
- Azithromycin 1 g orally, single dose.

General considerations

- Treatment of infected patients prevents important sequelae resulting from *C. trachomatis* infection and transmission to sexual partners and to newborns in the case of pregnancy
- Treatment should be effective (cure rate >95%), with high compliance due to low side-effects and an easy schedule
- Patients with chlamydial infection should be screened for other sexually transmitted infections.

Special considerations

- *Abstinence* from sexual intercourse for 7 days after single-dose therapy, or until completion of a 7-day regimen and until all current partners have received satisfactory treatment
- *Azithromycin* has shown equal efficacy to doxycycline in studies to date⁷⁻⁹. It is preferable if non-compliance with treatment is suspected¹⁰. For men azithromycin will generally be preferred. It is also effective for non-specific urethritis. It is not known whether doxycycline is more effective than azithromycin for women with asymptomatic ('silent') PID. Symptomatic PID should be excluded before recommending treatment for a woman. Transmission of syphilis may be reduced by rendering patients with concurrent syphilis non-infectious¹¹
- *Doxycycline* has a longer history of extensive use, and the advantage of lower cost
- *Erythromycin* is less efficacious than azithromycin or doxycycline, and gastrointestinal side-effects frequently discourage patients from complying with this regimen

- *Roxithromycin* and *clarithromycin* are alternative macrolide antibiotics with high tissue concentrations and are tolerated better by patients due to their lower side-effect profiles
- *Ofloxacin* is similar in efficacy to doxycycline and azithromycin, but is more expensive and offers no advantage in dosing. Other quinolones are not reliably effective against chlamydial infection
- *Compliance* with therapy is related to providing information about mode of transmission of chlamydia, sequelae, importance for the partner, diagnosis and treatment schedule and side-effects.
- Possible indications for follow-up examination are:
 - Reassurance of the patient
 - Asymptomatic *C. trachomatis* infection
 - Persistence of symptoms
 - Suspected non-compliance of the patient
 - Possibility of re-infection
 - After therapy with erythromycin (higher risk of treatment failure)
- Timing of test of cure: Culture, EIA/ELISA and DNA hybridization test: 2 weeks after the end of therapy; NAA assays: 3–4 weeks after the end of therapy
- Rescreening women several months following treatment may be an effective strategy for detecting re-infection with chlamydia and preventing morbidity in some populations, e.g. adolescents.

Special considerations for pregnant women

- Doxycycline and ofloxacin are contraindicated in pregnant women
- Erythromycin estolate is contraindicated during pregnancy because of drug-related hepatotoxicity
- Preliminary data suggests that azithromycin may be safe and effective. However, there are insufficient data to recommend its routine use in pregnant women
- Repeat testing 3 weeks after completing therapy is recommended, because none of these regimens are highly efficacious and the frequent side-effects of erythromycin may discourage patient compliance with this regimen.

Special considerations for HIV-infected persons

- Persons with HIV infection and chlamydial infection should receive the same treatment as patients without HIV infection.

Management of partners

- Patients should be instructed to refer their sex partners for evaluation, testing and treatment
- Partners whose last sexual contact with the index patient was within 60 days of onset of the index patient's symptoms or diagnosis, should be evaluated, tested, and treated
- Partners at risk should be informed, invited to attend for evaluation and offered epidemiological treatment even if tests for chlamydial infection are negative
- Patients and their partner(s) should be instructed to abstain from sexual intercourse until they all have completed correct treatment (7 days after a single-dose regimen or after completion of a 7-day regimen).

Follow up

- Microbiological follow up is not strictly necessary after treatment with doxycycline or azithromycin, but may be useful for health education, follow-up partner notification, and providing reassurance

CHLAMYDIAL INFECTIONS AMONG INFANTS

C. trachomatis infection of neonates results from perinatal exposure to the mother's infected cervix. Infants born to mothers with untreated chlamydia are at high risk for infection, and should be followed for the development of infection and treated appropriately. Prenatal screening of pregnant women can prevent chlamydial infection among neonates. Asymptomatic infections of the oropharynx, genital tract and rectum also occur in neonates.

Clinical diagnosis

- Initial *C. trachomatis* perinatal infection involves the mucous membranes of the eye, oropharynx, urogenital tract, and rectum
- *C. trachomatis* infection is recognized by signs of conjunctivitis developing 5–12 days after birth
- *C. trachomatis* is a common cause of subacute, afebrile pneumonia with onset from 1–3 months of age. Characteristic signs are repetitive staccato cough with tachypnoea, hyperinflation and bilateral diffuse infiltrates on a chest X-ray.

Laboratory diagnosis

- Conjunctivitis specimens for culture isolation and non-culture tests should be obtained from the everted eyelid using a Dacron-tipped swab or the swab specified by the manufacturer's test kit
- Pneumonia: specimens should be collected from the nasopharynx for chlamydial testing
- Tissue culture remains the definitive standard for chlamydial pneumonia; tracheal aspirates and lung biopsy specimens should be tested if available
- The microimmunofluorescence test for *C. trachomatis* antibody is useful for diagnosis

of chlamydial pneumonia in neonates but is not widely available. An IgM antibody titre 1:32 is strongly suggestive of *C. trachomatis* pneumonia.

Indications for testing

- Clinical symptoms of conjunctivitis
- Clinical symptoms of pneumonia.

Treatment

Recommended regimen for conjunctivitis and pneumonia

- Erythromycin 50 mg/kg/day orally divided into 4 doses for 10–14 days
- Topical antibiotic therapy alone is inadequate for treatment of chlamydial infection and is unnecessary when systemic treatment is administered.

Follow up

- Follow up of infants to determine resolution is recommended. The efficacy of erythromycin treatment is approximately 80%. A second course of therapy may be required. The possibility of concomitant chlamydial pneumonia should be considered.

General considerations

- Ocular exudate from infants being evaluated for chlamydial conjunctivitis should also be tested for *N. gonorrhoeae*
- A specific diagnosis of *C. trachomatis* infection confirms the need for chlamydial treatment not only for the neonate, but also for the mother and her sex partner(s).

Ocular prophylaxis

- Neonatal ocular prophylaxis with silver nitrate solution or antibiotic ointments is ineffective in preventing perinatal transmission of chlamydial infection from mother to infant. However, ocular prophylaxis with those agents does prevent gonococcal ophthalmia.

CHLAMYDIAL INFECTIONS AMONG CHILDREN

Sexual abuse must be considered a cause of chlamydial infection among preadolescent children, although perinatally transmitted *C. trachomatis* infection of the nasopharynx, urogenital tract, and rectum may persist beyond 1 year.

Diagnosis

Because of the potential for a criminal investigation and legal proceedings for sexual abuse, diagnosis of *C. trachomatis* among preadolescent children requires the high specificity provided by isolation in cell culture. The cultures should be confirmed by

microscopic identification of the characteristic intracytoplasmic inclusions, preferably by fluorescein-conjugated monoclonal antibodies specific for *C. trachomatis*. Although the result of a cell culture for chlamydia is the only test usually accepted by legal authorities, it should be remembered that this test is of low sensitivity. A combination of cell culture plus NAA assay is recommended.

Treatment

Recommended regimen

- Children <45 kg: erythromycin 50 mg/kg/day divided into 4 doses for 10–14 days
- Children who are 8 years-of-age or who weigh >45 kg but who are <8 years-of-age: use the same treatment regimens for these children as the adult regimens of azithromycin.

Follow up

- Follow-up cultures are necessary to ensure that treatment has been effective
- The effectiveness of erythromycin treatment is approximately 80%; a second course of therapy may be required.

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MANAGEMENT OF SPECIFIC INFECTIONS

European guideline for the management of genital herpes

Herpes Simplex Virus Special Interest Group of the Medical Society for the Study of Venereal Diseases, United Kingdom:

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INTRODUCTION

First infection with either herpes simplex virus type 1 (HSV-1) or type 2 (HSV-2) is termed primary infection and results in either symptomatic disease at the site of viral entry (i.e. around the mouth or around the genital area) or asymptomatic and hence unrecognized disease. In addition there may be systemic symptoms as with other acute viral illnesses. Following infection, the virus becomes latent in the local sensory ganglion, periodically reactivating to cause symptomatic lesions or asymptomatic, but none the less infectious, viral shedding. Genital herpes can be caused by either HSV-1 (the usual cause of oro-labial herpes) or by HSV-2. Infection with either virus can cause an identical initial illness. However, subsequent recurrence frequency is greater for HSV-2 than HSV-1 disease¹.

Transmission risk

Risk of transmission appears to be greatest during lesional recurrences or prodrome. Patients should be advised to abstain from sexual contact during this time. Transmission can occur in the absence of lesional recurrence as a result of subclinical viral shedding. Efficacy of condoms to prevent sexual transmission has not been formally assessed. Risk of transmission is greater from men to women than vice versa. Prior infection with HSV-1 reduces the HSV-2 seroconversion risk in serodiscordant couples^{2,3}.

DIAGNOSIS

Clinical

Although classical genital herpes can be recognized by the presence of typical papular lesions progressing to blister and ulcer formation, associated with local adenitis and in recurrent cases preceded by prodromal symptoms, the features in many

patients can be highly variable⁴. The majority of patients will suffer from atypical lesions where signs may be easily confused with other genital infections or dermatoses. Clinical diagnoses alone in atypical cases should, whenever possible, be avoided.

Laboratory

Virus detection and characterization

The confirmation of the infection is essential and characterization of its strain is recommended for diagnosis, prognosis-counselling and management.

Laboratory diagnosis is based on direct detection of HSV from genital lesions which may be atypical (Table 1). The quality of samples is critical and specimens should be collected using swabs directly from the base of the lesion. HSV is a labile virus and successful virus culture depends on maintaining the cool chain (4°C), rapidly transporting specimens to the laboratory and avoiding freeze-thaw cycles. Local factors (laboratory resources, distance) should be considered in deciding on the testing strategy. The stage of the lesion will determine the success of virus detection⁵⁻⁷. Negative diagnostic tests do not exclude infection. Patients may require reassessment on a number of occasions for a definitive diagnosis to be made.

Serology

Most currently available commercial tests for HSV antibodies are not type-specific (e.g. complement-fixation test (CFT) and many enzyme immunoassays (EIAs)). These tests are rarely of value in the management of genital HSV. However, type-specific commercial assays are becoming available and are either EIAs based on glycoprotein G (gG₁, gG₂) or Western blot.

Type-specific immune responses can take 8-12 weeks to fully develop following primary infection.

Full serological assessment of genital HSV requires access to both HSV-1 and 2 type-specific antibody assays, because of the high proportion of cases due to HSV-1 infection. HSV-1 type-specific assays are consistently less sensitive and specific than those for HSV-2.

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Table 1. Detection of HSV in lesions, available tests

	Virus culture	Antigen detection (immuno-fluorescence on smears) Tzanck test	Antigen (e.g. EIA)	Nucleic acid (e.g. PCR)
Source	Swabs/scraping	Smear/tissue section	Swabs/scraping	Swabs/scraping
Sensitivity	High, >90% from lesions	Low	80%	Highest
Specificity	High	High	High	Controls for cross-contamination important
Advantages	Allows virus typing and antiviral sensitivity using monoclonal antibodies testing	Inexpensive	Cost and speed	Allows virus typing high sensitivity
Disadvantages	Sample transport, labour-intensive, expensive	Insensitive	Insensitive, no viral typing	No commercial assay available, expensive

The value of screening all STD clinic attenders or antenatal patients for HSV antibodies has not been established.

Tests should be fully evaluated for sensitivity, specificity, reproducibility against virus culture and/or validated established tests (e.g. Western blot) before being introduced into clinical practice.

The value of these tests for patient management has not been fully assessed but they are likely to contribute in cases with recurrent genital ulceration of unknown cause, for counselling patients with initial episodes of disease and the asymptomatic partners of patients with HSV-2 infection⁸.

As adverse psychological sequelae may follow the identification of an asymptomatic chronic infection, protocols for use of type-specific antibody of tests need to be developed in individual centres.

MANAGEMENT

First-episode genital herpes

Indications for therapy

First episodes of genital herpes are frequently associated with a prolonged disease course. Untreated, many patients suffer general and local complications. Therapy can be highly effective and should be instigated on clinical suspicion alone.

Antivirals

Patients presenting within 5 days of the start of the episode, or while new lesions are still forming, should be given oral antiviral drugs. Aciclovir, valaciclovir and famciclovir are all effective in reducing the severity and duration of episode^{9,10}.

Topical agents are less effective than oral agents.

The only indication for the use of intravenous therapy is when the patient is unable to swallow or tolerate oral medication because of vomiting. Intravenous therapy does not alter the natural history of genital herpes infection¹¹.

The regimens recommended are (all for 5 days):

- Aciclovir 200 mg 5/day, or
- Famciclovir 250 mg 3/day, or

- Valaciclovir 500 mg 2/day.

Choice should be made by individual clinicians taking cost of therapy and likely compliance into account.

Supportive measures

Saline bathing and the use of appropriate analgesia is recommended. Caution should be exercised in using topical anaesthetic agents because of the potential for sensitization.

Counselling

Counselling of patients with first-episode genital herpes should include a discussion of the following topics: possible source(s) of infection, natural history including risk of subclinical viral shedding, future treatment options, risk of transmission by sexual and other means, risks of transmission to the foetus during pregnancy and the advisability of the obstetrician and midwife being informed, sequelae of infected men infecting their uninfected partners during pregnancy, the possibility of partner notification.

Management of complications

Hospitalization may be required for:

- Urinary retention
- Meningism
- Severe constitutional symptoms
- Adverse social circumstances.

If catheterization is required, suprapubic catheterization is preferred both on theoretical grounds (to prevent ascending infection) and practical grounds.

Special situations — HIV-positive patients with first-episode genital herpes

There are no controlled trials on duration and dose of treatment. Some clinicians advocate a 10-day course of treatment.

Follow up

Patients are followed up until the episode has resolved and counselling is considered complete.

Further follow up may be required to exclude other causes of genital ulceration that may be co-existent.

Patients should be invited to reattend should recurrences be problematic.

Recurrent genital herpes

Indications for therapy

Genital herpes recurrences are self-limiting and generally cause minor symptoms. Decisions about how best to manage clinical recurrences should be made in partnership with the patient. Management strategies include supportive therapy only, episodic antiviral treatments and suppressive antiviral therapy. The most appropriate strategy for managing an individual patient may vary over time according to recurrence frequency, symptom severity and relationship status. For most patients management will need to be supportive only, with simple local measures such as saline bathing or topical petroleum jelly being adequate.

Episodic antiviral treatment

Oral aciclovir, valaciclovir and famciclovir are effective at reducing the duration and severity of recurrent genital herpes. The reduction in duration is a median of 1–2 days for most patients^{12–14}. Valaciclovir is no more or less effective than aciclovir¹⁵. Famciclovir has not been compared with aciclovir. Famciclovir and valaciclovir have not been compared. Both famciclovir and valaciclovir have a twice-a-day dosing regimen which is easier to take than a 5-a-day regime. It is likely that patient-initiated treatment started early in an episode is most likely to be effective. Valaciclovir aborted one in 10 lesional recurrences when initiated by patients early in the course of an episode¹³.

The recommended regimens are all for 5 days:

- Aciclovir 200 mg 5 a day or
- Valaciclovir 500 mg twice daily, or
- Famciclovir 125 mg twice daily, plus supportive measures including saline bathing, petroleum jelly.

Suppressive therapy

All trials of suppressive therapy have been done in patients with a recurrence rate equivalent to ≥ 6 recurrences/annum. However, it is likely that patients with a lower rate of recurrence will also reduce their rate of recurrence with treatment. The frequency of recurrence at which it is worth starting suppressive therapy is a subjective issue and needs to balance the frequency of recurrence against the cost and inconvenience of treatment.

Patients with culture-proven genital herpes who have a recurrence rate equivalent to ≥ 6 episodes of genital herpes annually are highly likely to experience a substantial reduction in recurrence frequency on suppressive antiviral therapy.

Experience with suppressive antiviral therapy is most extensive with aciclovir¹⁶. Safety and resis-

tance data on patients on long-term therapy now extends to over 11 years of continuous surveillance.

Recommended regimens

The optimal daily dose of suppressive aciclovir therapy is 800 mg. The only published clinical dose-ranging study concluded that a dose of 200 mg 4 times a day was clinically superior to 400 mg twice daily. However, ability to comply with a 4 times a day regimen should determine prescribing decisions for individual patients.

Suppressive therapy using famciclovir (250 mg twice daily) has only been compared with placebo and not against the current standard of care¹⁷. Twice-daily valaciclovir (250 mg twice daily) has been shown to be as effective as twice-daily aciclovir (400 mg twice daily)¹⁵ in all patients. Patients with less frequent recurrences (<10 per annum) may be adequately suppressed on once-daily valaciclovir (500 mg once daily). Patients with more frequent disease (>10 attacks per year) require higher doses of once-daily valaciclovir to maintain control (1000 mg once daily). Once-daily aciclovir does not suppress genital herpes recurrences.

Therapy should be discontinued after a maximum of a year of continuous antiviral therapy to reassess recurrence frequency. Twenty per cent of patients will experience a reduction in recurrence frequency compared with pre-suppression symptomatic levels. The minimum period of assessment should include two recurrences. It is safe and reasonable to restart treatment in patients who continue to have an unacceptably high rate of recurrence.

Short courses of suppressive therapy to prevent clinical symptoms may be helpful for some patients (e.g. for holidays, exams, etc.).

Viral shedding and transmission on suppressive therapy

Subclinical shedding of infectious virus occurs in some individuals with genital HSV-1 and/or HSV-2. Viral shedding is more likely to occur in patients with genital HSV-2 infection, in the first year after infection or in individuals with frequent symptomatic recurrences. In one study, aciclovir 400 mg twice daily substantially reduced both the number of women with subclinical viral shedding and the number of days on which viral shedding occurred^{18,19}. The evidence in men is awaited. The effect of antiviral drugs on rate of sexual transmission has not been established.

SPECIAL SITUATIONS

Management of herpes in immunocompromised individuals

Although rare in immunocompetent individuals, clinically refractory lesions due to genital HSV are a major problem in patients with severe immunodeficiency, including late-stage HIV diseases. The algorithm in Figure 1 is modified from a paper

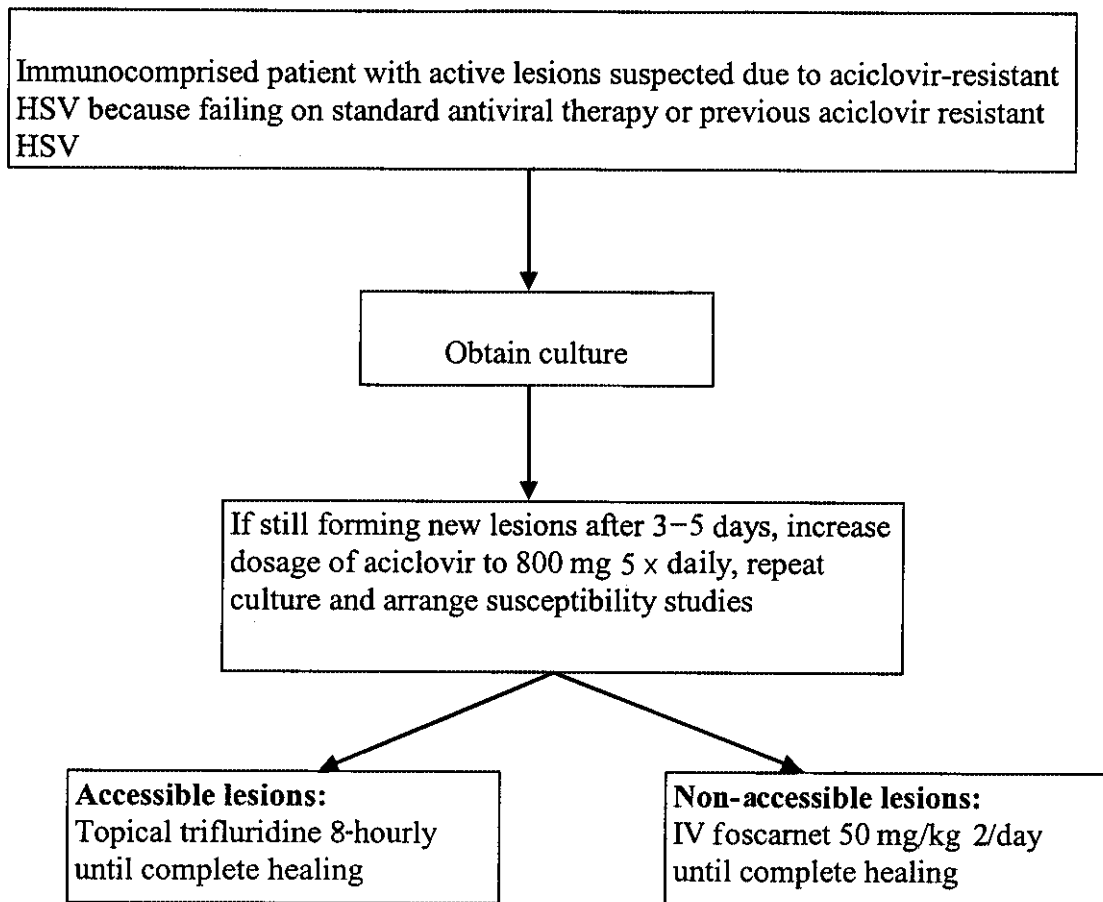


Figure 1. Algorithm for the treatment of herpes in immunocompromised patients

published following a consensus symposium on the management of resistant herpes simplex²⁰.

In addition there is evidence from a randomized, double blind, placebo-controlled trial that cidofovir gel (0.1% or 0.3% applied once daily for 5 days), achieves complete healing or >50% decrease in lesional area in up to 50% of patients. However cidofovir has only been compared with placebo and not against current standard of care (foscarnet or trifluridine)²¹.

Suppressive antiviral therapy

There is no evidence to suggest that immunocompromised patients on suppressive therapy for frequently recurring genital herpes need other than the standard regimen.

Management of partners

There is no evidence on which to base recommendations for partner notification. On an individual basis it may be appropriate to offer to see partners to help with the counselling process. Partner notification in relation to pregnancy is discussed below.

It is worth bearing in mind the following points when counselling patients.

- Asymptomatic shedding plays a major role in the transmission of HSV infection
- Partner notification is an effective way of detecting asymptomatic individuals when combined with type-specific antibody testing²²
- Up to 50% of asymptomatic HSV-2 seropositive women can be taught to recognize genital herpes recurrences after counselling. It may be possible to prevent transmission by educating patients to recognize symptomatic recurrences²³
- Although there is no definitive evidence that either antiviral treatment or patient education/counselling alters transmission rates of HSV at a population level, it seems logical to increase awareness of the diagnosis in patients when appropriate, with the aim of preventing further onward transmission.

Management of pregnant women with first-episode genital herpes

First and second trimester acquisition

- Management of the woman should be in line with her clinical condition and will often

- involve the use of either oral or intravenous aciclovir in standard doses
- Providing that delivery does not ensue, the pregnancy should be managed expectantly and vaginal delivery anticipated
- Continuous aciclovir in the last 4 weeks of pregnancy may prevent recurrence at term and hence the need for delivery by Caesarean section²⁴.

Third trimester acquisition

- Caesarean section should be considered for all women, particularly those developing symptoms within 6 weeks of delivery, as the risk of viral shedding in labour is very high
- If vaginal delivery is unavoidable, aciclovir treatment of mother and baby may be indicated.

Management of pregnant women with recurrent genital herpes

- Sequential cultures during late gestation to predict viral shedding at term are not indicated²⁵
- Caesarean section to prevent neonatal herpes should not be performed in women who do not have genital lesions at delivery
- Symptomatic recurrences of genital herpes during the third trimester will be brief; vaginal delivery is appropriate if no lesions are present at delivery
- The benefits of obtaining specimens for culture at delivery, in order to identify women who are asymptotically shedding HSV, are unproven.

Management of women with genital lesions at onset of labour

- There is evidence that the risks of vaginal delivery for the foetus are small and must be set against risks to the mother of Caesarean section²⁶.

Note: None of the antiviral drugs is licensed for use in pregnancy. There is most experience with aciclovir, which should therefore be used in preference to famciclovir or valaciclovir if clinically indicated.

Prevention of acquisition of infection

Any strategy for prevention of neonatal herpes needs to involve both parents.

- All women should be asked at their first antenatal visit if they or their partner have ever had genital herpes
- Female partners of men with genital herpes, but without a history of genital herpes, should be strongly advised not to have sex at the time of lesional recurrence. Conscientious use of condoms during pregnancy may diminish risk of acquisition

- Pregnant women should be advised of the risk of acquiring HSV-1 as a result of orogenital contact
- Identical susceptible women by means of type-specific antibody testing has not been evaluated in terms of costs and benefits
- All women, not just those with a history of genital herpes, should undergo careful vulval inspection at the onset of labour to look for clinical signs of herpes infection
- Mothers, staff and other relatives/friends with active oral lesions should be advised about the risk of postnatal transmission.

Management of the neonate

Babies born to mothers with first-episode genital herpes at the onset of labour

- HSV culture of urine and stool, from the oropharynx, eyes and surface sites to allow early identification of infected babies
- The potential benefits and risks of starting intravenous aciclovir without waiting for the results of these cultures should be discussed
- If aciclovir is not started immediately the neonate should be closely monitored for signs of lethargy, fever, poor feeding or lesions.

Babies born to mothers with recurrent genital herpes at the onset of labour

- One set of specimens for viral culture collected after delivery may help with early identification of infection
- Parents should be advised to report early any signs of infection (lethargy, fever, poor feeding or lesions).

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MANAGEMENT OF SPECIFIC INFECTIONS

European guideline for the management of anogenital warts

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INTRODUCTION

Condylomata acuminata 'condylomas' are benign anogenital warts caused by human papillomavirus (HPV), genotypes 6 and 11 being found in >90% of cases¹. Patients with visible warts may be infected simultaneously with oncogenic 'high-risk' HPVs such as types 16 and 18, which mostly give rise to subclinical lesions associated with intraepithelial neoplasia (IN) and anogenital cancer^{1–3}.

DIAGNOSIS

Clinical

Multifocal occurrence

Lesions tend to appear in areas that are traumatized during intercourse⁴ and may be solitary but generally comprise from 5 to ≥ 15 lesions of 1–10 mm diameter. Warts may coalesce into large plaques, which is particularly common in immunosuppressed individuals and in diabetics.

In uncircumcized men, the preputial cavity (glans penis, coronal sulcus, frenulum, inner aspect of the foreskin) is most commonly affected, while in circumcised men the shaft of the penis is often involved⁵. Warts may also occur on the scrotum, groin, perineum and anal area. In females, lesions affect the fourchette, labia minora, labia majora, clitoris, urethral meatus, perineum, anal region, vestibule, introitus, hymen, vagina and ectocervix^{2,3,6}. The urethral meatus is affected in 20–25% of males and 4–8% of females^{2,4}. Anal warts are seldom found proximal of the dentate line. Intraanal warts are most common when receptive anal intercourse has been practised⁷.

Multiform morphology

Colour varies from pinkish-raspberry to salmon-red (non-keratinized warts), greyish-white (heavily

keratinized lesions), and ashen-grey to brownish-black (pigmented lesions). Condylomas tend to be non-pigmented, but if so, are mostly seen on pigmented skin (labia majora, penile shaft, pubis, groin, perineum and anal area)^{8,9}.

Lesional types

Condylomas can be distinguished into three major types:

Accuminate warts predominate on mucosal epithelium, such as the preputial cavity, urinary meatus, labia minora, introitus, vagina, cervix, anus and anal canal, but may affect intertriginous areas as well (groin, perineum and anal area). These digitate projections have highly vascularized dermal cores producing typical punctuated and/or loop-like patterns unless the vessels are hidden beneath pronounced keratinization.

Papular warts being most common on keratinized epithelium (outer foreskin, penile shaft, scrotum, lateral vulva, pubis, perineum and perianal area) are often hyperkeratotic or pigmented, lack the finger-like surface irregularities of acuminate warts and are associated with differential diagnostic considerations. Pigmented, leukoplakia-like and brownish-red papules signify bowenoid papulosis.

Macular lesions may reveal their presence on mucous membranes due to subtle colour variations such as greyish-white, pinkish-red or reddish-brown.

Intraepithelial neoplasia: bowenoid papulosis and Bowen's disease¹⁰

Bowenoid papulosis (BP) and Bowen's disease (BD) are visible lesions associated with oncogenic HPV types, most commonly HPV 16, that exhibit full-thickness intraepithelial neoplasia (IN-III). These conditions are distinguished on clinical grounds, patient age being most important; BP appears at 25–35 years and BD at 40–50 years or over. BP presents as maculopapular lesions

exhibiting a smooth velvety surface; the colour tone on mucous membrane sites is brownish- or salmon-red, greyish-white, and on cutaneous sites ashen-grey to brownish-black^{8,11}.

'Giant condyloma' (Buschke-Löwenstein tumour)

This is a very rare variant of HPV 6 and 11-associated disease, characterized by aggressive down-growth into underlying dermal structures. A complex histological pattern may exist with areas of benign condyloma intermixed with foci of atypical epithelial cells or well differentiated squamous-cell carcinoma. Diagnosis of Buschke-Löwenstein tumour often requires multiple surgical biopsies, computed tomography or magnetic resonance imaging⁹.

Physical and psychosexual implications

Anogenital warts are disfiguring and can impact sexual lifestyle. They cause feelings of anxiety, guilt, anger and loss of self-esteem and create concerns about future fertility and of cancer risk^{12,13}. Physical symptoms may include inflammation, fissuring, itching, bleeding or dyspareunia⁹.

Clinical evaluation

The goal of investigation is to ensure appropriate diagnosis and treatment and to minimize psychosexual sequelae. By removing the disease, the risk of transmission of HPV for that individual is probably reduced. Tests for concurrent STDs should be offered according to local policy. Prior to therapy, recording the distribution of solitary, multiple or plaque lesions at various sites allows for subsequent evaluation of clearing of original lesions and the identification of any new lesions that develop.

In both sexes a careful inspection of the outer genitals is performed with a clear and powerful light. Use of a lens is highly recommended to detect small lesions.

In women 25% also have acuminate cervical and/or vaginal warts; up to 50% flat lesions or cervical intraepithelial neoplasia (CIN) lesions, the majority being low-grade^{2,3}. About one-third of women with vulval intraepithelial neoplasia (VIN) have associated CIN and/or vaginal intraepithelial neoplasia (VAIN)^{14,15}. Accordingly, all women with anogenital warts should have a speculum examination to identify the presence of coexisting vaginal and/or cervical warts. In contrast to vulvar lesions, routine histological assessment is mandatory whenever cervical lesions are treated, the biopsy being taken under colposcopic guidance.

Meatoscopy

The meatal lips can be everted using cotton wool swabs but a fuller inspection of the fossa navicularis in men is performed by 'meatoscopy' using a small speculum (spreader) or an otoscope; about 5% of cases require urologic investigation for

adequate delineation of the proximal border. As a rule, the posterior urethra of male patients is not involved without previous or simultaneous growth of meatal warts.

Anoscopy

Concurrent perineal and perianal warts exist in one third of patients, so inspection of these areas must be carried out, and anoscopy up to the dentate line should be carried out if anal warts are present.

The acetic acid test¹⁶

Following application of 5% acetic acid, HPV lesions may turn greyish-white for a few minutes. As the test has poor specificity it is only recommended for use in specialist settings where colposcopy is available, and is not recommended for screening purposes. However, it may be valuable in identifying lesions for targeted biopsy and for demarcating lesions during surgical therapy. False-positive results are commonly due to inflammatory conditions (e.g. lichen sclerosus et atrophicus, lichen planus, psoriasis, balanoposthitis and vulvovaginitis, eczema, genital herpes and traumatic microabrasions) and give rise to ragged, irregular acetowhite borders. There may be varying degrees of underlying hyperaemia and capillaries lack the vascular punctuation suggestive of HPV.

Differential diagnosis

Differential diagnoses include a range of dermatologic conditions including molluscum contagiosum, fibroepitheliomata and seborrhoeic keratoses^{8,9,16}. However, the most frequent condition causing confusion in males is physiologic pearly penile papules developing in adolescent men, when 1-3 rows of discrete non-coalescing 1-2 mm papules appear circumferentially on the verge of the glans and/or symmetrically in the parafoveal area. They are small, with a smooth surface, do not coalesce and do not show the vascular pattern of condylomas. In females, condylomas must be distinguished from physiologic regularly shaped and non-coalescing, mostly symmetrical papillae appearing on the inner surface of the labia minora and in the vestibule ('micropapillomatosis labialis'). Sebaceous glands of the foreskin and vulva are often seen in normal individuals as multiple, discrete, greyish-yellow, non-indurated lesions on the inner aspect of the prepuce and labia minora.

Laboratory histology

Biopsy is unnecessary for newly occurring, multiple, acuminate lesions (see Box 1) but recommended in atypical cases for differential diagnostic purposes or in any cases where the benign nature of a papular or macular lesion is unclear, such as conspicuous BP, BD and giant condylomas.

Biopsy is performed under local infiltration anaesthesia, preferably 10 minutes after applying

Box 1. Diagnosis — key points

- (1) Routine histology is unnecessary for newly occurring, multiple, acuminate warts in patients younger than 35 years
- (2) Differential diagnostic aspects generally exist for papular and macular lesions, as well as for warty lesions in patients over the age of 35–40, when routine biopsy is encouraged
- (3) HPV typing of anogenital warts does not add information of clinical use
- (4) The acetic acid test may be valuable for delineation of disease prior to biopsy and surgical treatment

topical anaesthesia, using a punch biopsy, an excision technique, or biopsy forceps.

MANAGEMENT

General

A reasonable expectation of therapy is cure, or at least long-lasting remission from warts and/or symptoms. The principal shortcoming of available therapies is that no method necessarily eradicates warts, maintains clearance and eliminates the virus; recurrence rates, including new lesions at previously treated or new, remote sites, are often 20–30%. All therapies are associated with local skin reactions including itching, burning, erosions and pain. Some regimens require multiple physician office visits and thus are not convenient for the patient.

Recommended regimens

In the formulation of these guidelines we have reviewed and considered those produced recently by national groups in the UK and US^{17,18}. We have also evaluated the evidence that supports our treatment recommendations using grades developed by the Agency for Health Care Policy and Research (see Tables 1 and 2)¹⁹. Our recommended treatment modalities are as follows.

Home therapy

- Podophyllotoxin (0.15% cream or 0.5% solution)
- Imiquimod (5% cream).

Clinic/office therapy

- Electrosurgery/laser/curettage/scissors excision
- Cryotherapy
- Trichloroacetic acid.

Clinicians who treat patients should be knowledgeable about, and have available, at least one home therapy and one clinic/office therapy. Choice of therapy depends on the morphology and extent of warts and should be made by mutual agreement between the physician and the patient. The average patient has a relatively small number of warts that can eventually be eliminated with most modalities. Patients with limited disease (1–5 warts) may benefit from simple office therapy. As warts regress spontaneously in some patients, no treatment is an option for warts at any site.

Home therapy

- Podophyllotoxin 0.5% solution and 0.15% cream (level Ib, grade A).

Podophyllotoxin, a purified extract of the podophyllum plant, binds to cellular microtubules, inhibits mitotic division and induces necrosis of condylomas that is maximal 3–5 days after administration. Erosions occurring as the warts

Table 1. Levels of evidence

Level	Type of evidence (based on AHCPR 1992) ¹⁹
Ia	Evidence obtained from meta-analysis of randomized controlled trials
Ib	Evidence obtained from at least one randomized controlled trial
IIa	Evidence obtained from at least one well-designed controlled study without randomization
IIb	Evidence obtained from at least one other type of well-designed quasi-experimental study
III	Evidence obtained from well-designed non-experimental descriptive studies, such as comparative studies, correlation studies and case-control studies
IV	Evidence obtained from expert committee reports or opinions and/or clinical experience of respected authorities

Table 2. Grading of recommendations

Grade	Recommendation (based on AHCPR 1994) ¹⁹
A (Evidence levels Ia, Ib)	Requires at least one randomized, controlled trial as part of the body of literature of overall good quality and consistency addressing the specific recommendation
B (Evidence levels IIa, IIb, III)	Requires availability of well-conducted clinical studies but no randomized clinical trials on the topic of recommendation
C (Evidence level IV)	Requires evidence from expert committee reports or opinions and/or clinical experience of respected authorities Indicates absence of directly applicable studies of good quality

necrotize are shallow and heal within a few days^{20,21}.

Each course of podophyllotoxin treatment comprises self-application twice daily for 3 days, followed by 4–7 rest days. Use of 0.5% podophyllotoxin solution is convenient for penile warts. However, vulvar and anal warts are more feasibly and efficiently treated with 0.15% podophyllotoxin cream when digital self-examination and tactile sensations facilitate the application procedure.

In uncircumcised males 70–90% of acuminate warts disappear after 1–2 courses of 0.5% podophyllotoxin solution, and 60–80% of patients become free of penile warts after 1–4 courses^{20,22}. Efficacy from the solution is lower for females and circumcised males, who experience a complete cure in less than 50% of cases^{23–25}. Clearance rates from 0.15% podophyllotoxin cream against vulva and anal warts are 60–80% when patients treat themselves for 1–4 courses^{26–28}. The recurrence rates with podophyllotoxin preparations are in the range of 7–38%^{23–25}. Warts that have not resolved after 4 courses should be treated by alternative means. Urinary meatus warts and warts on keratinized skin are often refractory²².

Up to 50–65% of patients using podophyllotoxin experience transient and acceptable burning, tenderness, erythema and/or erosions for a few days when the warts necrotize^{21,22}. Side-effects are usually only associated with the first course of therapy²². Occasionally, some pain occurs and uncircumcised men may experience transient problems in retracting the foreskin²¹.

- Imiquimod cream, 5% (level Ib, grade A)

Imiquimod (imidazoquinolinamine) is a nucleoside-like compound that by topical application to warts acts as an immune-response modifier, inducing local production of alpha and gamma interferon and recruitment of immune cells including CD4+ T cells. This process may be followed by an immune-induced wart regression that is accompanied by a reduction in HPV DNA^{29,30}.

Imiquimod cream, supplied in single-use sachets, is applied to the warts 3 times per week at bed-time and the area washed with mild soap and water the next morning. Treatment continues until wart clearance, or for a maximum of 16 weeks. Local reactions at the treatment site may occur and a rest period of several days may be taken if required.

In the pivotal clinical study, wart clearance was achieved by 56% of patients³¹. More women (77%) than men (40%) cleared their warts, the male study population comprising predominantly circumcised men³¹. Females had a shorter median time to clearance (8 weeks) compared to males (12 weeks). A low recurrent rate (13%) was found³¹.

The most common adverse reaction seen with imiquimod use is erythema, which occurred in 67% of patients in the pivotal clinical study, most of them mild to moderate in intensity³¹. Only 1% of

patients discontinued therapy due to local skin/application-site reactions³¹. However, in a more recent European study in uncircumcised males, reporting a clearance rate of 62% after 13 weeks of therapy, it was noted that 29% of the men required drug-free rest period(s) and that 6% discontinued due to erosions and/or burning³².

Special situations

Podophyllotoxin is contraindicated during pregnancy and women of childbearing age must use contraception or abstain from penetrative sexual activity during therapy. No studies have been conducted with imiquimod in pregnant women but the drug has not been found to be teratogenic in animal studies.

Skin reactions to podophyllotoxin generally develop on day 3 of therapy and to imiquimod after 3–4 weeks. Most resolve spontaneously within a drug-free period of a few days.

A rare but important complication is difficulty in retracting the foreskin due to painful erosions or oedema when treating multiple warts in the preputial cavity. Patients should be advised to return for medical supervision if this occurs. Daily symptomatic office therapy includes using saline rinses and a topical corticosteroid cream applied liberally under the foreskin until improvement.

Clinic/office therapy

- Surgical treatment

It is not possible to give clear directions for the surgical method of choice, as this is a matter of wart distribution, local tradition, and the clinical skills and experience of the physician. Surgery may be used as primary therapy, and the majority of patients can be treated under local anaesthesia. Routine use of local anaesthetic cream for 10–15 minutes is recommended prior to infiltration anaesthesia, significantly reducing discomfort from injections. Use of up to 100 mg lidocaine (as 5 ml of 2% or 10 ml of 1%) for infiltration gives rapid anaesthesia of the epithelium. Adrenaline as adjuvant reduces any bleeding but is contraindicated on the penis and in the clitoris region. Infiltration anaesthesia leads to separation and elevation of exophytic lesions facilitating accurate removal and sparing of uninvolved skin bridges for an optimal re-epithelialization process to follow. The end-point for the removal of tissue is the view of the underlying papillary dermis, which has a tanned chamois leather-like character. More excessive destruction may lead to fibrosis and scarring. When performed carefully, simple surgical approaches leave highly satisfactory cosmetic results, with the exception of some depigmentation, which is disadvantageous on very pigmented skin.

All lesions treated properly by surgery virtually disappear. However, regardless of the technique, 20–30% of patients will develop new lesions at the borders of the treated tissue and/or at remote sites^{33,34}.

- Scissors excision (level Ib, grade A), electro-surgery (Ib, A) and laser surgery (IIa, B)

Superficial scissors excision is useful when only a few lesions are present and may be assisted by diathermy to control bleeding and to destroy any conspicuous wart/tissue remaining after the excision.

Modern electrosurgical units utilize monopolar systems, where the electric current flows from the active electrode, the ball or the loop, through the patient's body to the return pad of the electrode.

Carbon dioxide laser emissions are in the infrared range. The energy emitted is focused to a specific spot by a system of mirrors and lenses, and is strongly absorbed by all types of tissue. Since total absorption of the carbon dioxide energy occurs in about 0.1 mm of the skin, very high power densities can be attained in small tissue volumes.

Both electro- and laser surgery should be performed with the use of surgical masks by the treatment team, and a smoke evacuator is required.

- Formal surgery

Extensive warts on the foreskin are sometimes best managed by circumcision rather than by other therapies, which may be associated with the risk of phimosis. Extensive intraanal warts are most conveniently removed under general anaesthesia by a proctologist. Also, in children and sensitive patients with extensive warts on the vulvoanal area general anaesthesia may be preferred for surgical procedures.

- Cryotherapy (grade Ib, level A)

The mechanism of action of cryotherapy is through epidermal and dermal necrosis and thrombosis of the dermal microvasculature. Treatment is usually performed at weekly intervals, a freeze-thaw-freeze technique used at each session. Open application of liquid N₂ can be performed either by spray device or by direct swab application, freezing the lesion and a margin of healthy skin for about 20 seconds. Closed cryoprobe systems utilize circulation of CO₂, N₂O or N₂, the probe gently pressed to the surface moistened with saline or lubricating jelly and freezing performed until a

freezing 'halo' occurs a few millimetres around the lesion.

Cryotherapy has the advantages of being simple, inexpensive and rarely causes scarring or depigmentation. Clinical studies report an efficacy range of 63–89%^{35,36}. However, application techniques are difficult to standardize and repeated sessions are often required.

- Trichloroacetic acid (TCA) 80–90% solution (grade Ib, level A)

TCA is a caustic agent that causes cellular necrosis. It is applied directly to the wart surface with a cotton-tip applicator. It is most suitable for small acuminate or papular warts but less efficacious for keratinized or large lesions. The initial response rate is 70–81% but recurrence rate is up to 36%^{17,37,38}. Multiple applications at 1–2 weekly intervals may be required but repeated therapy is not well tolerated because intense burning may be experienced for up to 10 minutes after applications. TCA is extremely corrosive and overzealous use may cause excessive pain, deep ulcerations into the dermis and scarring (see Box 2). A neutralizing agent (e.g. sodium bicarbonate) should be readily available in case of excess application or spills. When used optimally, a shallow ulcer forms that heals without scarring. TCA can be used safely during pregnancy.

Note. Another caustic agent, Solcoderm, manufactured in Switzerland and containing nitric, acetic, lactic and oxalic acids, is widely used in the Russian Federation for the topical treatment of anogenital warts. Although there are many anecdotal reports of its efficacy the authors and Editorial Board cannot comment on its usefulness due to a paucity of published evidence.

- Therapies not generally recommended

Due to several shortcomings including low efficacy and toxicity problems, routine use of interferons, 5-fluorouracil or podophyllin, is not recommended for use in the primary care setting. In the specialist setting, 5-fluorouracil is sometimes used against urethral warts³⁹ and alpha- and beta-interferons as adjuvant to surgery in problem cases^{40,41}. Podophyllin 20–25%, a non-standardized resin extract

Box 2. Treatment — key points

- (1) First-line treatment will achieve clearance in most patients within 1–6 months, although disease persists in up to one-third of patients
- (2) Home therapy can be proposed in most cases as first-line therapy for a first attack of acuminate warts. Acuminate warts respond in up to 90% but papular and macular lesions in only 50% of cases
- (3) Few, small lesions can be easily treated under local anaesthesia by scissors excision, diathermy, cryotherapy or TCA
- (4) TCA should not be used on large lesions and multiple sessions are not well tolerated by patients
- (5) Lesions occurring at new sites, during treatment or after clearance, do not necessitate a change of the treatment modality
- (6) Persistence or reappearance of the treated lesion is usually an indication to switch to another treatment modality
- (7) Patients should be evaluated regularly until the warts are cleared
- (8) Patients should be informed that periods of coital rest throughout the course of the therapy might reduce therapy-related symptoms such as pain or discomfort

Box 3. Patient counselling—key points

- (1) Patients should receive clear information, preferably written, as to the cause, treatment, outcomes and possible complications of anogenital warts
- (2) Reassure patients that although wart clearance may take 1–6 months and recurrences may occur, but complete clearance will occur sooner or later
- (3) Smokers with recalcitrant lesions should stop smoking as a correlation exists with wart development⁴⁹
- (4) Advise female patients about regular participation in cervical cytology screening programmes. Reassure that risk of cervical cancer is low and ample time exists for detection and removal of any CIN
- (5) Encourage patients to use barrier protection with new sexual contacts until successful treatment has been completed. The use of condoms within a stable relationship may not be needed as the partner will already have been exposed to the infection by the time of consultation. Condom use does not influence the outcome of HPV-associated morbidity once infection has become established in the individual
- (6) Due to long latency periods after transmission, the development of condylomas in only one partner in a steady relationship does not inevitably signify sexual contact outside that relationship
- (7) Current partners and, if advisable, other partners within the last 6 months, should be assessed for the presence of lesions and for education and counselling about STDs and their prevention

from the podophyllum plant, is inexpensive to produce but is associated with only moderate efficacy and appears to possess mutagenic properties *in vitro*^{20,42–44}. However, the *in vivo* implications of this finding are yet to be elucidated. Rarely, systemic toxicity has been described; applied in larger volumes severe systemic intoxication with fatal outcome has occurred leading to bone marrow suppression, central nervous system influence and cardiovascular crisis^{45–48}.

PATIENT COUNSELLING

Information and counselling are fundamental to proper management and need to be non-judgemental, supportive and focus on the nature of the disease, therapy expectations and a balanced perspective on sexual issues¹³ (see Box 3).

REFERRALS TO SPECIALISTS

The majority of anogenital warts can be dealt with by the non-specialist, both in terms of investigation and treatment. Referral to specialists is recommended as outlined in Table 3.

In early pregnancy warts may enlarge and multiply⁵⁰. Genital warts being present at delivery is associated with a risk quoted at 1 in 400 of the infants developing juvenile laryngeal papillomatosis (JLP)⁵¹. There is no proof that treatment

diminishes this risk, although reduction of viral burden would seem wise.

Immunosuppression as consequence of HIV infection and iatrogenically as a result of transplant grafting, is linked to a significant increase in multicentric and refractory condylomas, and of intraepithelial neoplasia^{52,53}. The US Centers for Disease Control recommend annual cytologic screening of HIV-positive women. We advocate the same policy for allografted women.

Genital warts in children may result from several modes of transmission⁵⁴; acquisition at birth by HPV transmission from the maternal genital tract, autoinoculation from finger warts, and non-sexual transmission from family members/carers. However, the possibility of sexual abuse must always be borne in mind. In one large series, child abuse was documented in 43% of the cases of genital warts⁵⁵. Children with anogenital warts should therefore be managed by a multidisciplinary team that includes a paediatrician.

SUMMARY

A wide range of therapies is available for the treatment of external genital warts. Some can be applied by the patient at home and others by the healthcare provider. The choice of therapy depends on the morphology and extent of the warts, the

Table 3. Referral to specialists

Problem	Specialist
Children	Paediatrician
Intraepithelial neoplasia	Gynaecologist/urologist/proctologist/ dermatologist with training in colposcopy
Vaginal warts	
Pregnant women	Obstetrician
Large widespread warts	Dermatovenereologist GU-medicine specialist Gynaecologist
Protracted course	
Differential diagnostic problems	
Intraurethral warts	Urologist
Anal warts	Dermatovenereologist Proctologist
Immunosuppression	Dermatovenereologist Gynaecologist

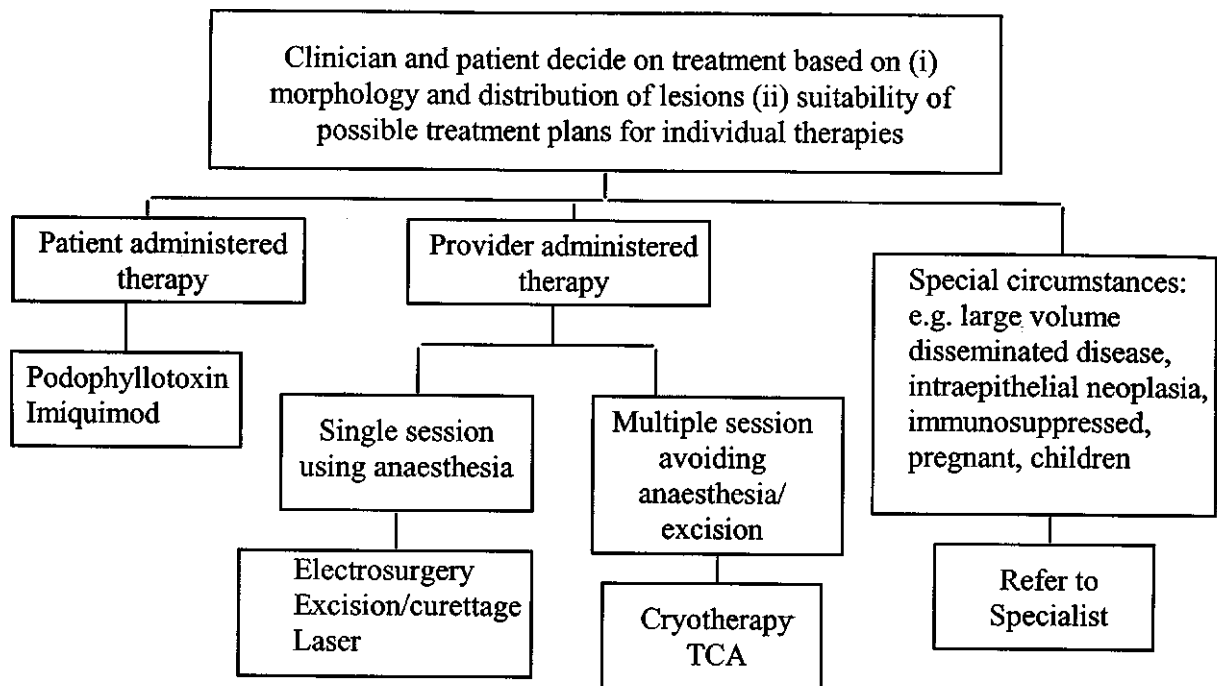


Figure 1. Algorithm for the treatment of external anogenital warts in the primary care setting

experience of the caregiver and the preferences of the patient.

The algorithm (Figure 1) summarizes our recommendations for therapy in the primary care environment. Irrespective of the therapy used, HPV may persist in the adjacent tissues, resulting in recurrences and the need for further courses of treatment. Such cases should be referred to a specialist, when colposcopically guided surgery and adjuvant interferon are further options.

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MANAGEMENT OF SPECIFIC INFECTIONS

European guideline for the management of hepatitis B and C virus infections

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HEPATITIS B VIRUS INFECTION

Hepatitis B is caused by a hepadna (DNA) virus. It is endemic world-wide, apart from isolated communities, with very high carriage rates (up to 20%) particularly in South and East Asia. High carriage rates (up to 10%) are also found in Central and South America, Africa and parts of Asia. The reported incidence of acute hepatitis B is 1 in 100 000 population in North-Western Europe, 6 in 100 000 in South-Western Europe, 22 in 100 000 in Central Europe and 92 in 100 000 in Eastern Europe, although the true incidence may be 6 times higher^{1,2}. There are estimated to be one million cases of acute hepatitis B and 90 000 new cases of chronic hepatitis B in Europe every year². Chronic carriage in the general population occurs in up to 5% in Southern Europe and in Northern Europe the rate is generally in the range 0.01–0.5%³. However, much higher carriage rates are found in certain sub-groups including intravenous drug users, homosexual men, female sex workers and immigrants from high-endemicity countries.

Transmission

Sexual transmission occurs in unvaccinated homosexual men and correlates with multiple partners, unprotected anal sex and also with oro-anal sex^{5,6,8–11}. Transmission also occurs after heterosexual contact, e.g. 18% infection rates for regular partners of patients with acute hepatitis B^{12–14}. Sex workers are also at higher risk^{7,15}.

Other routes are: parenteral (blood, blood products, drug-users sharing needles and syringes, needle-stick) and vertical (infected mother to infant)^{9,13,16–18}.

Sporadic infection occurs in people without apparent risk factors, in institutions for the mentally disabled and also in children in countries of high endemicity, but in these cases the means of transmission is poorly understood^{19,20}.

Diagnosis

Clinical

- Acute icteric hepatitis has an incubation period of 40–160 days

- Virtually all infants and children, and 10–50% of adults (especially HIV-positive) have asymptomatic acute infection^{21–24}
- In chronic infection there are often no symptoms or physical signs. After many years of infection, there may be signs of chronic liver disease^{10,24–27}.

Laboratory

See Table 1 for results of the applicable serology tests at each stage of infection^{10,23,28}.

Other tests

- Acute infection—serum amino-transferases (ALT and AST) raised: rarely >10 000 iu/l. Serum bilirubin: rarely >300 μ moles/l. Alkaline phosphatase <2 \times the upper limit of normal, except in cases complicated by cholestasis. Prothrombin time prolonged by up to 5 seconds; greater prolongation indicates developing hepatic failure
- Chronic infection—in most cases the only abnormality to be found will be mildly abnormal amino-transferase levels (usually <100 iu/l) and in many patients the liver function (LFT) will be normal.

Indications for HBV testing

Patient with acute icteric hepatitis

Test for hepatitis B surface antigen (HBsAg) (and liver function test, prothrombin time, urea and electrolytes). If HBsAg-positive, proceed to 'e' antigen (HBeAg), and anti-core IgM tests. Only in cases of doubt (e.g. HBeAg-negative) will hepatitis B virus DNA (HBV-DNA) need measuring, for interpretation see Table 1. Also test for hepatitis A and C.

Part of STD examination or screening

If local prevalence of hepatitis B carriage is <1% consider screening high-risk groups only (patients from highly endemic areas, homosexual men, sex workers, intravenous drug users, HIV-positive patients, sexual assault victims and sexual partners of HBsAg-positive patients or those in these risk groups)^{16,29–31}. If local prevalence of hepatitis B carriage is >1% consider testing all those attending for a STD screen.

Table 1. Serology

Stage of infection	Surface antigen (HBsAg)	'e' antigen (HBeAg)	IgM anti-core antibody	IgG anti-core antibody	Hepatitis B virus DNA	Anti-HBe	Anti-HBs
Acute (early)	+	+	+	+	+	-	-
Acute (resolving)	+	-	+	+	-	+ or -	-
Chronic (high infectivity)	+	+	-	+	+	-	-
Chronic (low infectivity)	or +	-	-	+	+	-	-
Resolved (immune)	-	-	-	+	-	+ or -	+ or -
Successful vaccination	-	-	-	-	-	-	+

Screening tests

Anti-hepatitis B core antibody (anti-HBc) is a suitable first screening test for natural immunity or carriage^{32,33}. An alternative screening strategy is to test for HBsAg initially (see Figures 1 and 2).

If after screening the patient is found to be non-immune, consider vaccination (see below)^{16,17,34,35}. If found to be a chronic carrier, consider referral for therapy^{24-27,29,36,37}.

Primary prevention/vaccination

- Hepatitis B transmission can be reduced by avoiding unprotected penetrative anal and vaginal sex and oro-anal contact, or by using condoms if the partner is HBsAg-positive or their status is unknown³⁸
- The World Health Organization recommends universal vaccination³⁸
- If universal vaccination is not pursued it should be offered to non-immune patients in most of the high-risk groups (see above)^{16,17,34,35}. The main exception is people born in countries of high endemicity but not at continuing risk, who are being screened primarily to detect chronic carriage²⁹⁻³¹. HIV-positive patients show a reduced response rate to the vaccine (approximately 40%)^{40,41} and can become anti-HBs-negative within a year⁴².
- The vaccination schedule for both the mono-valent and the combined hepatitis A+B vaccines is zero, one, and 6 months^{16,17,34,35}

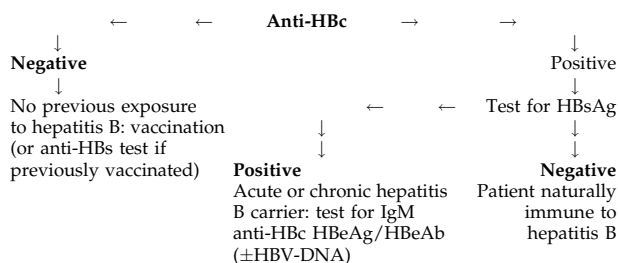


Figure 1. Flow-chart for hepatitis B screening using serum anti-HBc

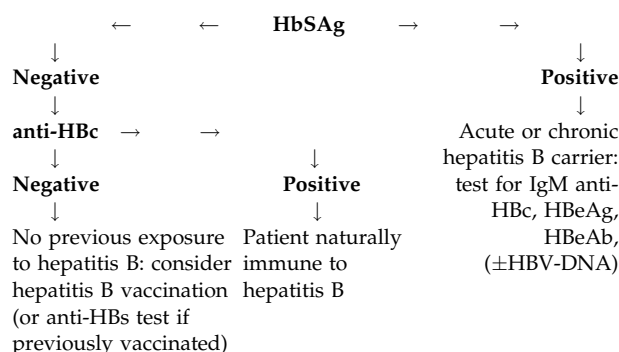


Figure 2. Flow-chart for hepatitis B screening using serum HBsAg

normally given as an intramuscular injection in the deltoid. Test for response (anti-HBs >10iu/l, but ideally >100iu/l) 4–12 weeks after the last dose^{16,17,34,35,43}

- An accelerated course of vaccine for those at very high risk (sexual or household contacts of HBsAg individuals) can be offered at zero, one, 2 and 12 months^{16,17,30,31,34,35}. Non- or poor responders usually respond to further doses (up to three injections), ideally given as a repeat course and show response rates up to 100%^{44,45}. New pre-S-containing vaccines show considerable promise as primary vaccination and for patients failing to respond to the standard vaccine⁴⁶⁻⁵⁰
- If the primary course of vaccination is incomplete, the missing doses of vaccine needed to complete the course can be given up to 4 years later without the need to restart the full course^{51,52}
- Recent evidence suggests that immunocompetent adults and children who have responded to a primary course of vaccine do not require booster doses for at least 15 years^{43,53-55}. However, immunocompromised patients, such as those with HIV or renal failure, require booster doses of vaccine when the anti-HBs level falls below 10iu/l^{42,43}.

Management of HBsAg-positive patients

- Patients should be advised to avoid unprotected sexual intercourse, including oro-anal contact, until they have become non-infectious or their partners have been successfully vaccinated (see below)^{9,10,12,16,29}
- Patients should be given a detailed explanation of their condition with particular emphasis on the long-term implications for the health of themselves and their partner(s), routes of transmission of infection (see below) and advised not to donate blood¹⁶
- Hepatitis B is a notifiable disease in many European countries
- If not performed already, screen for other sexually transmitted diseases in cases thought to have been sexually acquired or if otherwise appropriate^{8,15}
- Other tests such as liver biopsy (for assessment of chronic disease) should be performed by specialists in this field^{10,23–27}.

Indications for therapy of chronic infection

- Patients with HBeAg-positive infection for more than 6 months should be considered for alpha-interferon therapy, 5–20 mu by intramuscular or deep subcutaneous injection 3 times weekly for 12–32 weeks^{24–26,56,57}. Additional promising treatments, alone or in combination, include lamivudine, famciclovir, adefovir, thymosin alpha1 and ribavirin^{36,37,58,59,60–63}. Interferon alfa and lamivudine are the only agents licensed for this use at the time of writing. Response to interferon is highest (40–50%) in patients with adult-acquired infection with inflammatory liver disease (raised aminotransferase levels or chronic active hepatitis on liver biopsy) who are not immunocompromised^{24–26}. There is evidence that this treatment can be cost-effective and reduces long-term complications such as cirrhosis and liver cancer^{64–66}
- Lamivudine and famciclovir will suppress hepatitis B viral replication during therapy and may delay liver damage in HIV-positive patients. Cure is less certain in such patients and anti-viral resistance often develops in the hepatitis B virus, sometimes leading to exacerbation of the hepatitis^{67–69}
- Specific therapy is otherwise not indicated unless de-compensated liver disease ensues¹⁰, although hepatitis A vaccination should be offered due to the worse prognosis of dual infection⁷⁰.

Special situations

Pregnancy and breastfeeding

- Vertical transmission (mother to infant) of infection occurs in 65–90% of pregnancies where the mother is HBeAg-positive and in

about 10% of HBsAg-positive, HBeAg-negative mothers. Most (>90%) of infected infants become chronic carriers^{18,20,71}

- Infants born to HBsAg-positive mothers are vaccinated from birth, usually in combination with hepatitis B-specific immunoglobulin (HBSIg) 200 iu intramuscularly^{18,71}. This reduces vertical transmission by approximately 90%. However, if HBSIg is not available, vaccination alone prevents vertical transmission in 66–100%⁷¹. Infants should be tested for hepatitis B (HBsAg and anti-HBs) 4–6 weeks after the third dose of vaccine
- Infected mothers should continue to breast feed as there is no additional risk of transmission.

Management of partners and other contacts

- Partner notification should be performed and documented and the outcome documented at subsequent follow-up. Contact tracing to include any sexual contact (penetrative vaginal or anal sex or oro-anal sex) or needle-sharing partners, during the period in which the index case is thought to have been infectious^{30,31,72}. The infectious period is from 2 weeks before the onset of jaundice until the patient becomes HBsAg-negative. In cases of chronic infection trace contacts as far back as any episode of jaundice or to the time when the infection is thought to have been acquired, although this may be impractical for periods of longer than 2 or 3 years. Arrange screening for hepatitis B of children who have been born to infectious women if the child was not vaccinated at birth¹⁶
- If available, HBSIg 500 iu intramuscularly may be administered to a non-immune contact after a single unprotected sexual exposure or parenteral exposure or needle-stick injury if the donor is known to be infectious. This works best within 48 hours and is of no use after more than seven days^{16,73}
- An accelerated course of recombinant vaccine should be offered to those given HBSIg plus all sexual and household contacts (at zero, one, 2 and 12 months)^{16,17,30,31,34,35}
- Avoid sexual contact, especially unprotected penetrative sex, until vaccination has been successful (anti-HBs titres >10 iu/l)^{16,30,31,35,43}. Condoms will reduce the rate of transmission of hepatitis B if the patient and partner continue to have sex³⁸.

Follow up

- Acute infection: regular liver function tests (1–4 weekly) until normal. In view of the possibility of chronic infection, serum HBsAg should be repeated after 6 months even if the liver function tests (LFT) is normal^{10,22,23}

- Chronic infection: if untreated, patients should be regularly reviewed at intervals of one year or less, ideally by a physician with expertise in this disease^{10,22}
- Immunity after recovery from infection (surface antigen-negative) is lifelong in over 90%.

Hepatitis D (delta virus infection, HDV)

This is an incomplete RNA virus that requires the hepatitis B virus outer coat. It is only found in patients with hepatitis B. It is largely an infection of intravenous drug users and their sexual partners, but also female sex-workers, and sporadically other groups⁷⁴. Suspect HDV in hepatitis B particularly if the acute hepatitis is severe, if chronic hepatitis B carriers get a further attack of acute hepatitis or if the liver disease in chronic HBV is rapidly progressive^{10,21,23,75}. There is a high rate of fulminant hepatitis and progression of chronic hepatitis to cirrhosis^{21,22,75}. Diagnosis is confirmed by a positive anti-HDV antibody or HDV-RNA test^{23,28}.

HEPATITIS C VIRUS INFECTION

An RNA virus in the Flaviviridae family. It is endemic world-wide with high prevalence rates in South and East Asia and Eastern Europe^{4,76}. Prevalence rates vary from 0.06–1% in Northern European blood donors and 1.5–12% in Southern and Eastern Europe and up to 90% in intravenous drug users^{4,76–80}.

Transmission

- Parenteral spread accounts for the majority of cases through shared needles/syringes in intravenous users, transfusion of blood or blood products (pre-1990s), renal dialysis, sharing razors with infected individuals or needle-stick injury^{77,81–86}
- Sexual transmission occurs at a low rate (approximately 0.2–2% per year of relationship) but this rate increases if the index patient is also HIV-infected^{87–96}. There is an increased rate of carriage (2%) in homosexual men attending STD clinics but this is largely linked to HIV co-infection^{11,90,91}. There is also evidence of increased risk of infection in female sex workers^{7,97}, former prisoners, tattoo recipients and alcoholics^{98–100}
- Vertical (mother to infant) spread also occurs at a low rate (5% or less), mostly in HCV-RNA positive women¹⁰¹. Higher rates (up to 40%) are seen if the woman is both HIV- and HCV-positive^{83,87}, again predicted by high serum HCV-RNA levels^{102–105}
- Among blood donors, 50% of those with HCV infection do not admit to having risk factors^{81,106}

Diagnosis

Clinical

- Incubation period: 4–20 weeks for the uncommon cases of acute hepatitis
- The majority of patients (>80%) undergo asymptomatic acute infection^{82,83}
- <20% have acute icteric hepatitis^{82,83}, but fulminant hepatitis is particularly common after hepatitis A super-infection of chronic hepatitis C carriers¹⁰⁷
- Approximately 50–85% of infected patients become chronic carriers—a state which is normally asymptomatic but may cause non-specific ill health^{108–111}. Once established, the chronic carrier state rarely resolves spontaneously (0.02%/year)¹¹². Symptoms/signs are worse if there is a high alcohol intake or other liver disease^{113–116}. Significant liver disease can be present in the 35% of carriers who have normal serum aminotransferase levels^{82,83,117,118}.

Laboratory

- A screening antibody test (usually an enzyme-linked immunoassay, ELISA, to detect antibodies against the HCV surface proteins) is initially performed and if positive a second test, such as recombinant immuno-blot assay (RIBA), is often used to confirm infection^{28,119,120}. The older screening ELISA tests have a relatively high rate of false-positivity and should not be used alone, but third-generation ELISA test kits have a sensitivity and specificity of >95% and may not require RIBA confirmation^{121–123}. Patients who are RIBA- or ELISA-3-positive on 2 occasions, 6 months apart, can be assumed to have chronic infection
- Molecular biological techniques such as a reverse transcription polymerase chain reaction (RT-PCR) and branched chain DNA (bDNA) assays for viral RNA are also available to confirm infection but are generally not required as 85–95% patients positive for HCV antibody (RIBA or ELISA-3) will be HCV-RNA positive^{119,120,123–125}. Indications for HCV-RNA testing include patients with borderline-positive antibody tests and in cases of diagnostic doubt, e.g. to ascertain the relative contribution of several possible causes of hepatitis¹²². The RT-PCR and bDNA tests do not reliably detect all HCV genotypes and are subject to inter-laboratory variability^{119,120,124,125}
- HCV serology is usually positive (90%) 3 months after exposure, but can take as long as 9 months. Occasional cases of infection, proven by RT-PCR, do not result in positive antibody tests^{119,120,124}
- Acute infection—serum aminotransferase (AST and ALT) levels are raised but rarely >10 000 iu/l. Serum bilirubin rarely

>300 μ moles/l. Alkaline phosphatase <2 \times the upper limit of normal, except in cases complicated by cholestasis. Prothrombin time prolonged by up to 5 seconds; greater prolongation indicates developing hepatic failure

- Chronic infection—in most cases the only abnormality to be found will be mildly abnormal aminotransferase levels (usually <100 iu/l) and in many patients the LFT will be normal.

Indications for HCV testing

Patient with acute icteric hepatitis

Also measure LFT, prothrombin time, urea and electrolytes. If antibody tests negative, consider re-testing 3 and 9 months after onset of jaundice or test immediately using RT-PCR if available. Also test for hepatitis A and B.

Part of STD examination/screening

- Consider testing for hepatitis C in all intravenous drug users, especially if equipment has been shared, in haemophiliacs or other patients who received blood or blood products pre-1991 and in people sustaining a needle-stick injury if the donor HCV status is positive or unknown^{81,84–86,91,122,126,127}
- Other groups to be considered for testing are sexual partners of HCV-positive individuals, homosexual men, especially if HIV-infected, female sex workers, tattoo recipients, alcoholics and ex-prisoners^{7,90,91,94–99,126}. It may take 3 months or more for the anti-HCV test to become positive after exposure (see 'Diagnosis').

Primary prevention/vaccination

- It seems likely that if condoms are used consistently, then sexual transmission will be avoided³⁸
- Since 1991, donated blood has been screened for HCV, and blood products rendered incapable of transmitting infection, in most European countries¹²⁸
- Needle and syringe exchange schemes for drug users have led to a fall in parentally transmitted infections including HCV, HBV and HIV, although not consistently^{77,129–131}
- There is no effective vaccine currently available.

Management of HCV-positive patients

- Patients should be clearly advised not to donate blood, semen or organs and given advice on other routes of transmission (see below)¹³²
- Patients should be given a detailed explanation of their condition with particular emphasis on the long-term implications for the health of themselves and their partner(s). This should

be reinforced by giving them clear and accurate written information

- Acute hepatitis C infection is a notifiable disease in many countries
- If not performed already, screen for other sexually transmitted diseases in cases thought to have been sexually acquired or if otherwise appropriate^{8,15}
- Other tests such as liver biopsy (for assessment of chronic disease) should be performed by specialists in this field^{82,117,132,133}.

Indications for therapy

- Acute icteric hepatitis: there is some evidence that high-dose alpha- and/or beta-interferon given during the acute phase will reduce the rate of chronicity to only 10% or less^{122,134–136}
- Chronic infection: alpha interferon 5–10 MU by intramuscular injection 3 times a week given for 6–12 months will abolish chronic infection in approximately 20–30% of patients, and lymphoblastoid interferon alpha n1 appears to be better than recombinant interferon alpha 2b^{137–142}. The addition of ribavirin will increase the response rate to up to 50%^{139,143–146}. Thymosin alpha1 in combination with interferon also shows promise¹⁴⁷. Patients are more likely to respond to interferon treatment:
 - if they have less severe disease (low fibrosis index on liver biopsy)
 - low serum HCV-RNA levels (<2 million RNA copies/ml)
 - if they are infected with HCV genotypes other than type 1 or if they become HCV RNA-negative in the serum within 4 weeks of starting therapy^{137,138,143,145,146,148–153}
- There is evidence that treatment is cost-effective⁶⁴. HIV-positive patients respond well to treatment, especially if the CD4+ lymphocyte count is high (ideally >500 cells/mm³)^{154,155}
- It is unclear whether chronically infected patients with a normal LFT (tested on two occasions) should be treated^{117,122,156}. If they have liver damage demonstrated on biopsy, they may respond to therapy but less well than for patients with abnormal LFT^{117,156}
- Hepatitis A (and B if there are risk factors) vaccination should be offered to hepatitis C carriers due to the worse prognosis of dual infection^{70,107}. They should be informed of the increased risk of liver damage related to alcohol consumption^{122,157}.

Special situations

Pregnancy and breastfeeding

- There is at present no known way of reducing the risk of vertical transmission. Women should be informed of the potential risk of transmission in pregnancy (see transmission)^{89,132}

- There is no firm evidence for additional risk of transmission due to breastfeeding, except perhaps in women who are symptomatic with a high serum HCV viral load ($>2.5 \times 10^8$ RNA copies/ml)^{158,159}.

Management of partners

- Partner notification should be performed and documented and the outcome documented at subsequent follow up. Contact tracing to include any sexual contact (penetrative vaginal or anal sex) or needle-sharing partners, during the period in which the index case is thought to have been infectious⁷². The infectious period is from 2 weeks before the onset of jaundice in acute infection. If there was no acute infection, trace back to the likely time of infection (e.g. blood transfusion, first needle-sharing) although this may be impractical for periods longer than 2 or 3 years. Consider testing children born to infectious women⁸⁹. For other non-sexual contacts thought to be at risk, discuss with the public health physician
- There is currently no available vaccine or immunoglobulin preparation that will prevent transmission
- Sexual transmission should be discussed. It seems likely that if condoms are used consistently then sexual transmission will be avoided³⁸, but given the very low rate of transmission outside of HIV co-infection (see above), monogamous partners may choose not to use them.

Follow up

- Acute infection—regular LFT (1–4 weekly) until normal. In view of the possibility of chronic infection, serum anti-HCV or RT-PCR should be repeated after 6 months even if the LFT is normal¹²²
- Chronic infection—if untreated, patients should be regularly reviewed at intervals of one year or less, ideally by a physician with expertise in this disease¹²²
- Immunity is probably sub-type specific only—there are at least seven sub-types^{119,120,124}.

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MANAGEMENT OF SPECIFIC INFECTIONS

European guideline for the management of scabies

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Transmission of the mite (*Sarcoptes scabiei*) occurs by protracted direct body contact; although in crusted scabies (Norwegian scabies), transmission also occurs via infected clothing or bedding.

Mites are capable of burrowing into the stratum corneum of a contact person within one hour. Hypersensitivity to proteases in mite faecal matter generates both local and distant hypersensitivity reactions.

DIAGNOSIS

Clinical

- The main symptom is itch, which usually develops 2–6 weeks after infestation. In a re-infected person the itch recurs within 1–4 days
- Examination reveals characteristic silvery lines with a mean length of 0.5 cm, which may be seen in the skin where the mites have burrowed. Typical sites include between the fingers and on the sides of hands and feet, on wrists, extensor surface of the elbow, female nipples, penis and scrotum, anterior axillary folds
- Papules or nodules, which result from itching, often affect the genital area
- The clinical manifestations of crusted scabies are described below.

Indication for testing

This is important in, at least, the index patient before taking far-reaching epidemiological measures, e.g. epidemic in an institution:

- Direct microscopic examination of a potassium hydroxide mount of a superficial epidermal skin sample ('skin snip') obtained with a scalpel from the end of a burrow
- Experienced clinicians may probe a burrow with a needle to obtain material for direct microscopic examination
- Direct examination of skin for mites using an epiluminescence stereomicroscope has also been described¹.

MANAGEMENT

Indication for routine STD examination

- History of risk behaviour for STD in a sexually active patient with scabies.

Indications for therapy

- Characteristic clinical findings
- High-risk contacts: persons with protracted or frequent skin contact (e.g. via the hands) should be treated whether or not they have symptoms
- Low-risk contacts: persons with indirect contact (e.g. via bedding) only require treatment in cases of crusted scabies (see below).

Recommended regimens

Efficacy, tolerability and cost guide the specific choice of therapy. The quality of evidence comparing one treatment with another is poor^{2,3}. A Cochrane review has been performed⁴: one large and one small trial indicated no difference in the clinical cure rates of topical permethrin and lindane treatment, whereas treatment with permethrin had an advantage in two small trials. The data on topical treatment with benzyl benzoate, crothamiton, allethrin, malathion (and ivermectin) are limited. Oral treatment with ivermectin has been evaluated^{5–10}, but has been associated with deaths^{11–13}. It has not been licensed in any country for treatment of scabies in humans and is therefore only considered for the treatment of crusted scabies (see below) and when appropriate topical treatment is not possible.

- Permethrin 5% (once for 8–12 hours) is effective and well-tolerated^{14–16}, but cost can be a problem. In some countries permethrin 2.5% is used in children <5 years-of-age¹⁷, a policy not substantiated by published evidence
- Lindane 1% (once for 8–12 hours) is effective¹⁸, but may cause neurological side-effects because of absorption of the drug through skin^{15,16,19}. It is not available throughout Europe. Centers for Disease Control (CDC) guidelines recommend that it not be used in children aged <2 years²⁰. Netherlands

guidelines recommend that lindane be avoided in²¹: (a) premature children; (b) children below the tenth percentile of growth; (c) children with epilepsy; (d) children with pre-existent generalized skin disorders such as eczema

- Benzyl benzoate 25% (thrice, for 24 hours each day) appears to be effective, but is said to require application on three successive days²². One study combining benzyl benzoate 22.5% with disulfiram 2% showed cure after a single application²³. For children use of 10% benzyl benzoate is advocated in some countries^{17,22}. Benzyl benzoate may cause irritant dermatitis²²
- Sulphur (6–33%) in various preparations can act as an antiscabietic²⁴. It is effective, very cheap and safe, but stains clothing and requires application on three successive days for 24 hours each day
- Other options: (a) crotamiton 10%, but it appears to be less effective than permethrin and lindane^{3,17,25}; (b) allethrin, a synthetic pyrethroid^{17,26}; (c) malathion 0.5%^{27–30}.

Addendum on treatment procedure

- Before applying lindane: no bathing or shower before treatment unless the skin needs to be cleaned. If the patient does wash before treatment, one hour should elapse for the skin to dry properly before applying the lotion, because of increased absorption of lindane when applied to damp skin, and hence risk of toxicity
- Treatment instructions: patients should be provided with written instructions, which should include the amount of drug to be applied. Apply lotion/cream to the entire skin from the jawline downwards including all folds, groin, navel, external genitalia and the skin under the nails. In babies, the skin of the face and scalp should also be treated (transmission is possible from contact by breastfeeding). If the patient applies the lotion/cream

him/herself, the hands should not be washed after application. Attention should be given to application at the tips of the fingers and under the nails (especially in crusted scabies). If the lotion/cream is applied by someone without scabies, that person should wear (medical) disposable gloves. If there is any doubt as to whether or not a patient will apply the lotion/cream according to instructions, a second application is recommended, preferably soon after the first

- Hygienic measures: after completion of treatment, use fresh bedding and clothing. Potentially contaminated clothes and bedding should be washed at high temperature (>50°C) if possible, or may be kept in one or more plastic bags for at least 72 hours, because mites separated from the human host die within that time
- In some parts of Europe legal requirements dictate the choice of first-line treatment (see Table 1).

Special situations

Pregnancy/lactation

- Permethrin, benzyl benzoate (applied thrice), and sulphur (applied thrice) appear to be safe in pregnancy although the evidence tends to be anecdotal^{20,25,27,31}.

Crusted scabies (Norwegian scabies)

- Crusted scabies is seen in immunocompromised persons, e.g. AIDS patients^{32,33}, in persons with neurological disturbance and those confined to long-term institutions
- Clinical signs typically consist of hyperkeratotic/crusted plaques, papules and nodules, particularly on the palms of the hands and the soles of the feet, although areas such as the axillae, buttocks and scalp may also be affected. Occasionally there may be psoriasiform or eczematous lesions with fine, powder-like scaling and redness, generally on a dry skin

Table 1. Scabies treatment protocol options, as stated by law in the Russian Federation

Medication	Concentration		Number of applications/day (duration of medication)	Days of treatment	Hygienic measures: on day x
	Adults	Children			
Benzyl-benzoate	20%	10%	1 (24 hours)	Day 1 and 4	Day 5
Sulphuric ointment	20–33%	5–10%	1 (24 hours)	Day 1–5 (1–7)	Day 6 (8)
(I) Sodium hyposulphite (Na ₂ S ₂ O ₃ · 5H ₂ O) solution*	60%	40%	1	Day 1 and 2	Day 3
plus (II) Hydrochloric acid (HCl) solution*	6%	4%	1	Day 1 and 2	Day 3

Application of solution I should be followed, after allowing solution I to dry for ±10 minutes, by application of solution II

*Demianovitch method. The procedure can be repeated once after 3 days.

- Diagnosis by direct microscopy of skin samples is straightforward in view of the large numbers of mites and eggs in the scales
- Combined topical and oral treatment is thought to be the best option, if ivermectin is available (other oral antiparasitic drugs, i.e. thiabendazole and flubendazole, may also be effective^{3,34}). Topical treatment is with two applications of permethrin 5% or lindane 1% to the entire skin, including the head. Permethrin can be applied more than twice, if necessary. This may be alternated with keratolytic therapy, e.g. emollients or bathing. Oral treatment with ivermectin (total of 2–3 doses every 1–2 weeks) is given at a dose of 0.2 mg/kg
- Because of the increased risk of transmission to contact persons, strict isolation should be observed until cure is achieved. Care needs to be exercised with recently handled or used personal possessions. Active epidemiological measures to ensure treatment of all contacts are necessary
- Complication of crusted scabies: bacterial sepsis.

FOLLOW UP

- It should be explained to patients that after treatment some itching might persist for several weeks, especially in atopic individuals.
- Symptomatic relief may be obtained from a topical antipruritic, e.g. crotamiton and/or a topical corticosteroid.
- A test of cure (direct microscopy, not using potassium hydroxide, for living/moving mites) may be performed, especially in crusted scabies.

RESISTANCE

- Resistance to lindane, though rare, has been described^{35,36}. Biologically speaking, resistance can be expected with any drug if used frequently within a given population.

COMPULSORY NOTIFICATION

- In some European countries, scabies should be notified to the Health Authorities.

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MANAGEMENT OF SPECIFIC INFECTIONS

European guideline for the management of pediculosis pubis

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DIAGNOSIS

Clinical

- Nits and/or lice on hair
- Itching red papules
- Maculae cerulae (particularly on the lower abdomen and thighs).

Laboratory

- Microscopic examination of a nit or louse of *Pthirus pubis* if diagnosis uncertain.

MANAGEMENT

General

Screening for other STI is indicated.

Recommended regimens

The quality of evidence comparing one treatment with another is poor¹, and some of the recommendations are based on the treatment of head lice²⁻⁴.

- Malathion 0.5% lotion on dry hair, wash out 12 hours after application
- Permethrin 1% lotion⁵ on wet hair, wash out after 10 minutes
- Phenothrin 0.2% lotion on dry hair, wash out after 2 hours
- Carbaryl 0.5% and 1% on dry hair, wash out after 12 hours
- Decontaminate bedding/clothes by ordinary laundering
- Treatment may be repeated after one week if necessary.

Special situations

Pregnancy/lactation

Permethrin appears to be safe in pregnancy.

Lice in the eyelashes

- Vaseline eye patch reapplied twice daily for 8–10 days, or
- Remove lice with tweezers or forceps, or
- Apply permethrin 1% lotion with a cotton swab to the eyelashes, wash off after 10 minutes (permethrin does not irritate the eyes, but the eyelids should be kept closed throughout the treatment).

Management of partners

Always treat infected contacts, preferably simultaneously with the index patient.

FOLLOW UP

- After one, and if necessary 2 weeks. Look for lice
- Explain to patients that dead nits may remain adherent to the hairs, and need not be removed.

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MANAGEMENT OF SYNDROMES

European guideline for the management of urethritis

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INTRODUCTION

In men, a urethral discharge is characteristic of urethritis. However, physiological urethral discharge can occur in men, while urethritis can be present without an observable discharge. Men with urethritis may have symptoms of dysuria and/or irritation at the tip of the penis. More importantly some patients with an observable discharge will be unaware of it.

While the diagnosis of urethritis should be confirmed by demonstrating an excess of polymorphonuclear leucocytes (PMNLs) in the anterior urethra (through the use of urethral smears or first pass urine specimens (FPU)) this may not always be possible. Urethritis is described as either gonococcal, when *Neisseria gonorrhoeae* is detected, or non-gonococcal (NGU) when it is not. With the advent of chlamydial testing it has become apparent that a substantial proportion of NGU cases were due to this organism (chlamydial urethritis). Those cases in which neither chlamydia nor gonorrhoea are found are referred to as non-gonococcal, non-chlamydial urethritis or more succinctly as non-specific urethritis (NSU).

Importance

- Urethritis enhances the risks of both transmitting and acquiring HIV from sexual intercourse¹
- The organisms associated with urethral discharge, in particular *N. gonorrhoeae* and *Chlamydia trachomatis*, are a significant cause of infertility in women
- Urethritis can cause complications such as sexually acquired arthritis and, if the posterior urethra is involved, epididymitis and prostatitis^{2,3}.

AETIOLOGY

- *N. gonorrhoeae*
- For those cases not due to *N. gonorrhoeae* (NGU):
 - *C. trachomatis* causes 30–50%
 - *Ureaplasma urealyticum* and *Mycoplasma genitalium* probably cause NGU and account for 10–20% of cases, respectively

- Other aetiologies are identified less frequently. *Trichomonas vaginalis* has been reported in 1–17% of cases of NGU. It is likely that the relative importance of *T. vaginalis* as a cause of NGU depends on the prevalence of the infection within the community^{3–5}. *Neisseria meningitidis*, herpes simplex virus, *Candida* sp., bacterial urinary tract infection, urethral stricture and foreign bodies probably account for only a small proportion of cases (<10%)⁴. There is also a possible association with bacterial vaginosis
- Between 20–30% of men with NGU have no organism detected
- There is some evidence that the aetiology of asymptomatic urethritis, without an observable discharge, differs from that of symptomatic urethritis, with *C. trachomatis* being detected less frequently³.

It is assumed that the aetiological agents of sexually acquired male NSU could potentially cause genital tract inflammation in women, in particular pelvic inflammatory disease (PID). This is unquestionably the case with chlamydial and gonococcal infection, but remains to be substantiated for other causes. However, as the aetiology of PID is unknown in 40–60% of cases, this assumption remains a possibility.

It is important to note that a significant proportion of men with urethral infection due to *N. gonorrhoeae*, *C. trachomatis* or *T. vaginalis* will not have experienced a urethral discharge. While many such men will have urethritis on examination, these infections can be present without causing urethritis^{3,6}.

DIAGNOSIS

Clinical symptoms

- Urethral discharge
- Dysuria
- Penile irritation
- Asymptomatic.

Clinical signs

- Urethral discharge. This may only be present on urethral massage. A significant group of

- men with asymptomatic urethritis will have a discharge on examination
- Balano-posthitis: it is not known whether this is a non-specific cause of distal urethritis or sign of urethritis or both. The latter seems most likely
 - Epididymo-orchitis
 - Normal examination.

Complications

These are most frequently associated with gonococcal and chlamydial infections. For other causes of urethritis complications are infrequent and occur in fewer than 1% of cases.

- Epididymo-orchitis
- Sexually acquired reactive arthritis
- Reiter's syndrome.

See guidelines on chlamydia² and gonorrhoea⁷.

In gonococcal infection the discharge is usually more evident and purulent than that in NGU. Nevertheless, the severity of urethritis cannot differentiate reliably between gonococcal and non-gonococcal urethritis⁸.

Male patients complaining of urethral discharge and/or dysuria and/or penile irritation should be examined for evidence of discharge. If none is seen, the urethra should be gently massaged from the ventral part of the penis towards the meatus. This can be undertaken by the patient.

Laboratory

Microscopy available

The diagnosis of urethritis should be confirmed by demonstrating PMNLs in the anterior urethra as a discharge in men is not always pathological. The use of either a urethral smear or a first-pass urine specimen is a valid method of sampling. Both tests will identify cases missed by the other test.

- A Gram-stained urethral smear containing ≥ 5 PMNL per high-power ($\times 1000$) microscopic field (averaged over five fields with greatest concentration of PMNLs)⁹, and/or
- The identification of ≥ 10 PMNL per high-power ($\times 1000$) microscopic field (averaged over five fields with greatest concentration of PMNLs) on a Gram-stained preparation from a FPU specimen.

The sensitivity of the above tests is affected by how long the patient has not passed urine for. A duration of 4 hours is usually quoted.

- Gram stain for Gram-negative diplococci to exclude gonorrhoea. This has a sensitivity of $> 90\%$ in experienced hands.

Microscopy unavailable

- Mucopurulent or purulent discharge observable on examination^{10,11}, or

- Positive leucocyte esterase dipstick test on first-pass urine specimen¹¹, or
- Positive two-glass urine test¹²: the foreskin should be retracted fully and the patient asked to urinate into two clean specimen glasses, the first 10–20 ml, into one glass, the rest into the second. If the urine is hazy, add sufficient 5% acetic acid to dissolve the phosphate crystals which are responsible for the haze. When there is infection of the anterior urethra, the haze will persist in the first glass of urine due to the presence of pus cells, threads or flecks, but the second will be clear. If both glasses are abnormal, the infection also involves the posterior urethra, bladder or kidneys. This is most likely to indicate a bacterial urinary tract infection but may also represent severe urethritis often due to gonorrhoea or simply be due to the patient forgetting to void into two glasses and dividing the first glass into two.

Both the leucocyte esterase dipstick test and the two-glass urine test have reduced sensitivities compared to microscopy for detecting urethritis and are not recommended for the confirmation of NGU if microscopy is available¹¹.

Symptomatic patients, in whom no urethritis is detected

- Should be invited to attend for repeat confirmation having held their urine overnight
- Empirical treatment of these patients is not recommended unless they:
 - are at high risk of infection
 - are unlikely to return for repeat evaluation.

Investigations if available

- A urethral culture for *N. gonorrhoeae*
- *C. trachomatis* should also be sought (see guideline on chlamydia)
- Consider culture for *T. vaginalis*
- Consider culture for herpes simplex virus if ulceration is present.

MANAGEMENT

General advice

The following should be discussed and clear written information provided:

- A detailed explanation of what urethritis is and what causes it, with particular emphasis on the long-term implications for the health of the patient and their partner(s)
- Side-effects of treatment and importance of complying fully with it and what to do if a dose is missed
- The importance of their sex partner(s) being evaluated and treated
- Advise to abstain from sexual intercourse until they have completed therapy and their partner(s) have been treated

- Advice on safer sex.

Treatment

Unless a diagnosis of gonorrhoea can be definitively excluded by laboratory tests, the treatment of the patient with urethral discharge should include:

- Therapy for uncomplicated gonorrhoea and
- Therapy for NGU (which must cover possible chlamydial infection), and
- Treatment for *T. vaginalis* must be considered.

Recommended regimen for uncomplicated gonorrhoea

- Ciprofloxacin 500 mg stat plus treatment for NGU (see below)
- Antibiotics used for gonorrhoea may need to be varied according to local knowledge of antibiotic sensitivities.

Alternative regimens for *N. gonorrhoeae*

- Ceftriaxone 250 mg im
- Spectinomycin 2 g im
- Cefixime 400 mg¹³
- Amoxicillin 3 g plus probenidol 1 g (only to be used if sufficient local knowledge to conclude that penicillin resistance is <5%).

Increasingly, resistance of *N. gonorrhoeae* to ciprofloxacin is being detected. In some developing countries it is a significant problem. To avoid this occurring with ceftriaxone, cefixime and spectinomycin, these agents should ideally only be used when appropriate medical follow-up facilities are available (see below).

Recommended regimens for NGU

- Doxycycline 100 mg twice a day for 7 days
- Azithromycin 1 g orally in a single dose.

Alternative regimens for NGU

- Erythromycin (EC) 500 mg 4 times a day for 7 days
- Erythromycin (EC) 500 mg twice daily for 14 days
- Ofloxacin 200 mg 2 times a day or 400 mg once a day for 7 days
- Deteclon compound 300 mg 2 times a day for 7 days
- Tetracycline 500 mg 4 times a day for 7 days.

Recommended regimens for *T. vaginalis*¹⁴

- Metronidazole 2 g stat

Note: Patients taking metronidazole should be cautioned to avoid alcohol.

Compliance with therapy

There is evidence to show that in general compliance is improved if¹⁵:

- There is a positive therapeutic relationship between the patient and the doctor

- The medication is not more than twice daily
- The medication has a low side-effect profile
- The medication causes minimal interference with daily lifestyle.

MANAGEMENT OF PARTNERS

All sexual partners at risk should be assessed and offered epidemiological treatment. This needs to be handled sensitively and the confidentiality of the index patient maintained. The duration of look-back is arbitrary; 4 weeks prior to onset of symptoms is suggested for symptomatic men and up to 6 months for asymptomatic men.

The treatment regimen used should be as detailed for uncomplicated *C. trachomatis* infection. The regimen should also include treatment for gonorrhoea if such treatment was prescribed for the index patient.

- Details of all contacts should be obtained at the first visit. Consent should also be obtained to contact either the patient or his partners if tests for *C. trachomatis* or *N. gonorrhoeae* are found to be positive. This ensures that if the index patient does not reattend, he can be contacted and/or provider referral can be initiated for sexual contacts
- Female contacts of men with chlamydial urethritis should be treated regardless of whether chlamydia is isolated
- Concurrent treatment of the sexual partners of men with chlamydia-negative NGU may result in an improved response in some patients, and a possible reduction in female morbidity. There are reports of patient with persistent or recurrent urethritis being cured only after their sexual partner received appropriate treatment¹⁶
- No test is 100% sensitive for detecting *C. trachomatis* in men with NGU
- There is evidence that at least some men with 'chlamydia-negative' NGU have partners who are chlamydia-positive¹⁷.

FOLLOW UP

This is an important part of the management of 'urethral discharge', and should take place 7–14 days after initiating therapy. However, some patients may not return, emphasizing the importance of the initial consultation. Follow up has a number of objectives including:

- Following up on partner notification
- Reinforcing health education
- Providing reassurance
- Assessment of treatment compliance and efficacy
- Repeat urethral smear and FPU specimen to look for persistent urethritis (test of cure) may be advisable.

PERSISTENT/RECURRENT URETHRITIS

Persistent or recurrent symptoms or discharge may be due to:

- Poor compliance
- Reinfection
- Infection with a resistant strain of *N. gonorrhoeae*
- Infection with *T. vaginalis*
- Idiopathic—often the cause cannot be established
- There is no evidence that female partners of men with persistent/recurrent NGU are at increased risk of PID, provided they have been treated appropriately
- Persistent chlamydial infection is only rarely a cause, providing the patient and partner(s) have complied appropriately with treatment.

It is important that persistent infection with *N. gonorrhoeae* is identified and managed appropriately

Diagnosis of persistent/recurrent urethritis

Only proceed to formal diagnostic tests if:

- The patient is symptomatic, or
- The patient has an observable discharge on examination
- The patient had gonococcal urethritis.

Microscopy available

- As for 'urethral discharge', see above
- If no objective evidence of urethritis is detected, an early morning smear should be undertaken and if negative the patient reassured.

Microscopy unavailable

- As for 'urethral discharge', see above.

Management of persistent/recurrent urethritis

- Persistent gonorrhoea should be excluded. If microscopy is not available the patient should be referred for laboratory investigation
- Ensure patient has completed initial course of therapy, if not consider re-prescribing initial treatment
- Ensure sexual partner(s) have been treated and re-infection is not a possible cause
- If patient has no signs or symptoms, and providing chlamydia and gonorrhoea have been excluded, consider reassurance.

Treatment

- Erythromycin (EC) 500 mg 4 times a day for 2 weeks, with
- Metronidazole 2 g single dose or 400 mg twice a day for 5 days.

Some authorities would advocate the reduction of the erythromycin dose to 500 mg twice daily for 2 weeks in asymptomatic patients with no observable discharge¹¹.

- If gonorrhoea is present the antibiotic chosen will depend on local sensitivity patterns
- To avoid resistance developing the isolate should be cultured and the antibiotic sensitivities established
- There is only limited evidence on how best to manage patients who either remain symptomatic following a second course of treatment or who have frequent recurrences after treatment. A 3-week course of erythromycin 500 mg 4 times a day may help¹⁸. Urological investigation is usually normal unless the patient has urinary flow problems¹⁹. Chronic abacterial prostatitis, prostatadynia and psychosexual causes should be considered in the differential diagnosis¹⁸⁻²⁰
- There is no evidence to suggest that patients with urethritis who have no signs or symptoms after two courses of treatment are persistently infected. They should be reassured
- There is no evidence that re-treatment of an appropriately treated sexual partner is of benefit in the management of men with persistent urethritis. With recurrent urethritis an argument can be made for re-treating the sexual partner as it may represent re-infection. However this has not been evaluated in clinical studies.

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MANAGEMENT OF SYNDROMES

European guideline for the management of balanoposthitis

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INTRODUCTION

Balanoposthitis is defined as inflammation of the glans and/or prepuce. It comprises a disparate range of conditions, which are discussed individually below. Normal saline washes should be advised in all cases of balanoposthitis due to the association with poor hygiene. A range of other skin conditions may affect the glans penis. These include psoriasis, lichen planus, seborrhoeic dermatitis, pemphigus and dermatitis artefacta¹. In addition there are premalignant conditions including Bowen's disease and bowenoid papulosis, which form a continuum with penile intraepithelial neoplasia (PIN) but vary in clinical presentation and history².

CANDIDA BALANOPOSTHITIS

Diagnosis

Clinical

- Symptoms: erythematous rash, with soreness and/or itch (see Figure 1)
- Appearance: blotchy erythema with small papules which may be eroded, or dry dull red areas with a glazed appearance.

Laboratory

- Microscopy: of sub-preputial swab or tape ± KOH examination
- Sub-preputial culture
- Urinalysis for glucose.

Management

General

- Normal saline washes.

Indications for therapy

- Symptomatic candida balanoposthitis.

Recommended regimens

- Clotrimazole cream 1%³ twice daily
 - Miconazole cream 2%⁴ twice daily
 - Econazole 1%⁴ twice daily.
- } Equivalent

Alternative regimens

- Topical imidazole with 1% hydrocortisone twice daily if marked inflammation is present
- Fluconazole 150 mg stat orally⁵ in recalcitrant cases or with diabetes.

Special situations

- Nystatin cream 100 000 units/g if resistance suspected, or allergy to imidazoles.

Management of partners

Not strictly necessary. However, there is a high rate of candidal infection in sexual partners who should be offered screening if symptomatic.

Follow-up

Not required unless symptoms and signs are particularly severe or an underlying problem is suspected. If recurrence is a problem exclude factors predisposing to overgrowth of *Candida albicans*:

- Diabetes mellitus
- Broad-spectrum antibiotic use
- Immunodeficiency of any cause (e.g. steroid use, chemotherapy, HIV infection, other)
- Exclude re-infection from partner.

ANAEROBIC BALANOPOSTHITIS⁶

Diagnosis

Clinical

- Symptoms: foul-smelling discharge, swelling and inflamed glands
- Appearance: preputial oedema, superficial erosions, inguinal adenitis. This is also known as erosive bacterial balanitis. Milder forms also occur.

Laboratory

- Spirochaetes on dark-ground microscopy
- Fusiform/mixed bacterial picture on Gram stain
- Sub-preputial culture (to exclude other causes, e.g. *Trichomonas vaginalis*).

Management

Indications for therapy

- Symptomatic balanitis.

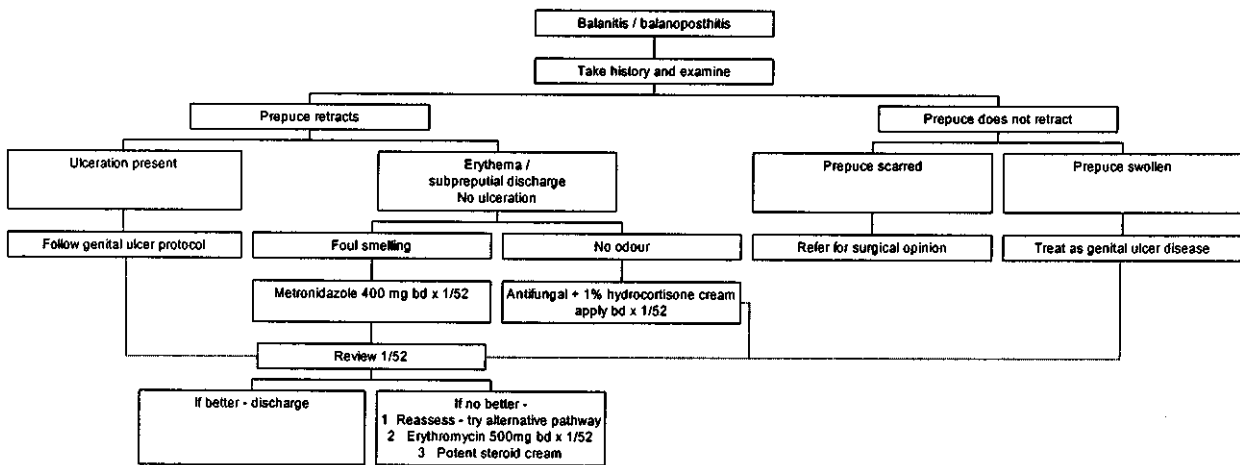


Figure 1. Balanoposthitis—(For all patients: • Advise on hygiene • Look for other STDs • Promote and provide condoms • Suggest partner attend if symptomatic.)

Recommended regimens

- Metronidazole 400 mg twice daily for one week.

Alternative regimens

- Co-amoxiclav 375 mg three times daily for one week
- Clindamycin cream applied twice daily until resolved.

Management of partners

Not strictly necessary. If genital ulcerative disease present, full sexually transmitted infection (STI) screening is required.

Follow-up

Only required if symptoms do not resolve, or other STI suspected.

AEROBIC BALANOPOSTHITIS¹

Diagnosis

Clinical

- Appearances will vary with the organism, from minimal erythema to fissuring and oedema.

Laboratory

- Sub-preputial culture: Streptococci Group A, *Staphylococcus aureus* and *Gardnerella vaginalis* have all been reported as causing balanitis. Other organisms may also be involved.

Management

Indications for therapy

- Symptomatic balanoposthitis.

Recommended regimens

- Depends on the sensitivities of the organism isolated
- Erythromycin 500 mg twice daily for one week will cover for staphylococcal and streptococcal infection
- Fusidic acid 2% cream 3 times daily will cover for staphylococci and other Gram-positive organisms.

Management of partners

Not strictly necessary.

Follow up

Only required if symptoms do not resolve, or other STI suspected.

HUMAN PAPILLOMAVIRUS (HPV) BALANOPOSTHITIS¹

Diagnosis

Clinical

- Clinical picture of diffuse erythema

Laboratory

- Characteristic histopathology on biopsy
- HPV detection and typing.

Management

Indications for therapy

- Symptomatic balanoposthitis.

Recommended regimens

- 5-Fluorouracil cream once/twice weekly
- Podophyllotoxin 0.15% cream twice daily for 3 days per week
- Treatment dependent on availability.

Management of partners

Not strictly necessary, although screening for other STI would be advisable. The patient should be informed of the risk of transmission of HPV to partner(s) and barrier protection discussed.

Follow-up

Assess response to therapy at 1 month. Further follow up only required if symptoms do not resolve, or other STI suspected.

LICHEN SCLEROSUS

Diagnosis

Clinical

- Typical appearance: white plaques on the glans, often with involvement of the prepuce. There may be haemorrhagic vesicles, and rarely blisters and ulceration. The prepuce may become phimotic, and the meatus may be thickened and narrowed.

Laboratory

- Biopsy: this initially shows a thickened epidermis which then becomes atrophic with follicular hyperkeratosis. This overlies oedema and loss of the elastin fibres, with an underlying perivascular lymphocytic infiltrate. Biopsy is the definitive diagnostic procedure.

Management

Indications for therapy

- Symptomatic balanoposthitis
- Thickening of the skin on the glans or prepuce.

Recommended regimens

- Potent topical steroids⁷ (e.g. clobetasol propionate or betamethasone valerate) applied once daily until remission, then gradually reduced. Intermittent use (e.g. once a week) may be required to maintain remission.

Alternative regimens

Procedures may be required for specific complications, but treatment of the underlying skin disease will still be required.

- Circumcision if phimosis develops
- Meatotomy for meatal stenosis.

Management of partners

Not required.

Follow up

Patients requiring potent topical steroids for disease control should be followed up regularly.

The frequency of follow up will depend on the disease activity and symptoms of the patient, but all patients should be reviewed by a doctor at least annually in view of the small risk (less than 1%) of malignant transformation⁸.

In addition, patients should be advised to contact the general practitioner or clinic if the appearance changes.

ZOON'S (PLASMA CELL) BALANITIS

Diagnosis

Clinical

- Typical appearance: well-circumscribed orange-red glazed areas on the glans with multiple pin-point redder spots, 'cayenne pepper spots'. This may be similar to erythroplasia of Queyrat, which is premalignant, and biopsy is advisable
- Patient usually over 30 years.

Laboratory

- Biopsy: epidermal atrophy, loss of rete ridges, lozenge keratinocytes and spongiosis, together with a predominantly plasma cell infiltrate subepidermally.

Management

Indications for therapy

- Symptomatic balanitis.

Recommended regimens

- Topical steroid preparations, with or without added antibacterial agents, e.g. Trimovate (clobetasone butyrate, oxytetracycline and nystatin) cream, applied once or twice a day⁹.

Alternative regimens

- Circumcision: this has been reported to lead to the resolution of lesions¹⁰
- CO₂ laser: this has been used to treat individual lesions¹¹—no clear evidence on equivalence.

Management of partners

Not required.

Follow up

- Dependent on clinical course and treatment used, especially if topical steroids are being used long term
- In cases of diagnostic uncertainty penile biopsy should be performed prior to discontinuing follow up, to exclude erythroplasia of Queyrat.

ERYTHROPLASIA OF QUEYRAT**Diagnosis***Clinical*

- Typical appearance: red, velvety, well-circumscribed area on the glans. May have raised white areas, but if indurated suggests frank squamous cell carcinoma.

Laboratory

- Biopsy: essential—squamous carcinoma *in situ*.

Management*Indications for therapy*

- Presence of lesion.

Recommended regimen

- Surgical excision: local excision is usually adequate and effective¹².

Alternative regimens

- | | | |
|--|---|------------|
| <ul style="list-style-type: none"> • Fluorouracil cream 5%¹³ • Laser resection¹¹ • Cryotherapy¹⁴ | } | Equivalent |
|--|---|------------|

Management of partners

Not required.

Follow up

Obligatory because of the possibility of recurrence. Minimum of annual appointments.

Auditable outcome measure

One hundred per cent of patients should have a biopsy.

CIRCINATE BALANITIS**Diagnosis***Clinical*

- Typical appearance: greyish-white areas on the glans which coalesce to form 'geographical' areas with a white margin. It may be associated with other features of Reiter's syndrome but can occur without.

Laboratory

- Biopsy: spongiform pustules in the upper epidermis, similar to pustular psoriasis
- Screening for STIs especially *C. trachomatis*.

Management*Indications for therapy*

- Symptomatic balanitis.

Recommended regimen

- Hydrocortisone cream 1% (or occasionally more potent topical steroids) for symptomatic balanitis⁹
- Treatment of any underlying infection.

Management of partners

If an STI is diagnosed the partner(s) should be treated as per the appropriate protocol.

Follow up

Required if persistent symptoms and/or associated STI.

FIXED DRUG ERUPTIONS**Diagnosis***Clinical*

- Typical appearance: variable but lesions are usually well-demarcated and erythematous, but can be bullous with subsequent ulceration
- History: a careful drug history is essential, as is a history of previous reactions. Common precipitants include tetracyclines, salicylates, phenacetin, phenolphthalein and some hypnotics
- Examine the oral and ocular mucosa
- Rechallenge: this can confirm the diagnosis.

Management*Indications for therapy*

- Symptomatic lesions.

Recommended regimen

- Topical steroids, e.g. 1% hydrocortisone applied twice a day until resolution¹⁵.

Alternative regimen

- Systemic steroids may be required if the lesions are severe.

Management of partners

Not required.

Follow up

Not required after resolution. Patients should be advised to avoid the precipitant.

IRRITANT/ALLERGIC BALANITIDES**Diagnosis***Clinical*

- Typical appearance: very variable. Appearances range from mild erythema to wide-spread oedema of the penis

- History: symptoms have been associated with a history of atopy or more frequent genital washing with soap. In a very small number of cases a history of a precipitant may be obtained
- Patch tests: useful in the small minority in whom true allergy is suspected.

Laboratory

- Biopsy: may show non-specific inflammation.

Management

Indications for therapy

- Symptomatic balanoposthitis.

Recommended regimen

- Avoidance of precipitants, especially soaps¹⁶
- Emollients—aqueous cream: applied as required and used as a soap substitute¹⁵
- Hydrocortisone 1% applied once or twice a day until resolution of symptoms.

All the above should be used in combination.

Management of partners

Not required.

Follow up

Not required, although recurrent problems are common and the patients need to be informed of this.

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MANAGEMENT OF SYNDROMES

European guideline for the management of vaginal discharge

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INTRODUCTION

Three common infections are associated with vaginal discharge—bacterial vaginosis, trichomoniasis and candidiasis¹. Vaginal discharge may also be caused by a range of other physiological and pathological conditions such as vulvar dermatoses or allergic reactions². These need to be considered if tests for specific infections are negative. Many of the symptoms and signs are non-specific. Occasionally cervical infection caused by chlamydia or gonorrhoea may result in vaginal discharge. Testing for chlamydia and gonorrhoea should be performed in those at risk of infection [see guidelines on the management of chlamydia (p. 30) and gonorrhoea (p. 27)].

BACTERIAL VAGINOSIS

This is the commonest cause of abnormal vaginal discharge in women of child-bearing age. It is characterized by an overgrowth of predominantly anaerobic organisms (*Gardnerella vaginalis*, *Prevotella* spp., *Mycoplasma hominis*, *Mobiluncus* spp.) in the vagina, leading to a replacement of lactobacilli and an increase in vaginal pH³. It is not regarded as sexually transmitted. It can arise and remit spontaneously in women regardless of sexual activity.

VAGINAL TRICHOMONIASIS

Trichomonas vaginalis (TV) is a flagellated protozoon, which in adults is almost exclusively sexually transmitted. Due to site specificity, infection can only follow intravaginal or intraurethral inoculation of the organism.

CANDIDIASIS

Vulvovaginal candidiasis is caused by *Candida albicans* in 90% of women (remainder other species e.g. *Candida glabrata*). An estimated 75% of women will experience at least one episode during their lifetime. 10–20% of women are asymptomatic vaginal carriers⁴.

DIAGNOSIS

Clinical

Although symptoms are not specific, some symptoms are more characteristic for one condition over another (Table 1).

There are characteristic physical findings associated with each infection (Table 2), but appearances cannot be fully relied upon and atypical presentations are common.

Indications for testing

The indications for testing for vaginal pathogens are:

- Change in 'normal' vaginal discharge
- Finding of TV on cervical cytology
- Diagnosis of TV in sexual partner
- Failure of vaginal discharge to respond to empirical treatment
- Failure of vulval pruritis to respond to empirical antifungal treatment.

Laboratory

The definitive diagnosis of each infection is based upon laboratory tests. A sample of the discharge is removed from the vaginal wall with a swab (Table 3). The type of fibre is not important. Direct microscopy can be done immediately at the clinic.

Criteria for diagnosis of bacterial vaginosis (BV)

- Amsel criteria⁵ (the presence of three of the following criteria is required):
 - thin white-grey homogenous discharge (sometimes frothy)
 - pH of vaginal fluid > 4.5
 - release of fishy odour on adding alkali (1% or 10% KOH) ('whiff test')
 - clue cells present on direct microscopy.
- Nugent criteria⁶: an alternative is to use a Gram-stained vaginal smear. This relies upon estimating the relative proportions of bacterial morphotypes to give a score between 0 and 10. A score of < 4 is normal, 4–6 is intermediate and > 6 is BV.

Table 1. Symptoms associated with vaginal infections

Bacterial vaginosis	Trichomoniasis	Candidiasis
Approx. 50% asymptomatic	10–50% asymptomatic	10–20% asymptomatic
Discharge	Offensive vaginal discharge	Vulval itching
Fishy odour	Vulval itching	Vulval soreness
	Dysuria	Vaginal discharge (non-offensive)
	Rarely, low abdominal discomfort	Superficial dyspareunia

Table 2. Signs associated with vaginal infections

Bacterial vaginosis	Trichomoniasis	Candidiasis
Thin, white homogenous discharge, coating walls of vagina and vestibule	Vulval erythema Vaginitis Vaginal discharge in up to 70%, frothy and yellow in 10–30% Approx. 2% ('strawberry' cervix) cervicitis to naked eye 5–15% no abnormal signs	Vulval erythema Vulval fissuring Vaginal discharge may be curdy (non-offensive) Satellite skin lesions Vulval oedema

Table 3. Microscopic findings on examination of vaginal secretions

	Bacterial vaginosis	Trichomoniasis	Candidiasis
Vaginal pH	>4.5	>4.5	4.0–4.5
Saline microscopy of vaginal discharge from lateral vaginal wall	Clue cells	Motile flagellated protozoa (40–80% cases)	Pseudohyphae (40–60% cases)
Gram stain of vaginal discharge from lateral vaginal wall	See Nugent criteria		Spores/pseudohyphae (up to 65% of symptomatic cases)
Whiff test—release of fishy odour on adding alkali (10% KOH)	Positive	Usually positive	Negative

Criteria for diagnosis of TV^{7–9}

- Direct observation of the organism by a wet smear (normal saline) or acridine orange stained slide from the posterior vaginal fornix (will diagnose 40–80% cases)
- Trichomonads are sometimes reported on cervical cytology where the sensitivity is approximately 60%, but there is a high false-positive rate. In such cases it is prudent to confirm the diagnosis by a vaginal swab
- Culture media are available and will diagnose up to 95% of cases.

Criteria for diagnosis of vaginal candidosis^{10,11}

- Vaginal pH of 4–4.5
- Absence of smell (in 'whiff test' on speculum and in amine odour test on slide)
- Yeasts or pseudohyphae on wet preparation (40–60% positive) of vaginal discharge
- Yeasts or pseudohyphae on Gram stain (up to 65% positive) of vaginal discharge
- Vaginal culture positive for a yeast species (if predominant vulval symptoms take vulval swab).

MANAGEMENT

General

Accurate diagnosis is important for the selection of appropriate specific treatment and, in the case of TV, appropriate management of sexual partners. As TV is a sexually transmitted organism, screening for co-existent infections should be undertaken. Sexual abstinence should be advised until treatment of all partners is completed.

Indications for therapy

BV

- Symptoms
- Positive direct microscopy with/without symptoms in some pregnant women (those with a history of prior idiopathic preterm birth or second-trimester loss)
- Women undergoing some surgical procedures
- Optional: positive direct microscopy in women without symptoms. They may report a beneficial change in their discharge following treatment.

TV

- Positive test for trichomoniasis regardless of symptoms
- Epidemiological treatment of sexual partners.

Candida

- Symptomatic women found to have candida on either microscopy or culture
- Asymptomatic women do not require treatment.

Recommended regimens**TV and BV^{1,3,12}**

- Metronidazole 400–500 mg orally twice daily for 5–7 days (first choice), or
- Metronidazole 2 g orally (single-dose).

With metronidazole, alcohol should be avoided because of the possibility of a disulfiram-like (Antabuse) reaction.

Most strains of TV are highly susceptible to metronidazole and related drugs. There is a spontaneous cure rate in the order of 20–25%. Due to the high rates of infection of the urethra and paraurethral glands in women, systemic chemotherapy should be given to effect a permanent cure. The single dose has the advantage of improved compliance and being cheap. However, there is some evidence to suggest that the failure rate is higher, especially if partners are not treated concurrently.

Vaginal candidiasis¹⁴

Topical therapy provides effective treatment for vaginal candidiasis. Treatment with azoles results in relief of symptoms and negative cultures among 80–90% of patients after treatment is completed, whether administered orally or topically. Only topical preparations should be used during pregnancy.

Topical treatments include:

- Clotrimazole vaginal tablet 500 mg once or 200 mg once daily for 3 days (500 mg weekly may be useful or recurrent candidiasis)
- Miconazole vaginal ovule 1200 mg as a single dose or 400 mg once daily for 3 days
- There are a large number of other preparations available.

Oral preparations include:

- Fluconazole 150 mg as a single dose
- Itraconazole 200 mg twice a day for 1 day
- Fluconazole 100 mg a week may be useful for recurrent candidiasis.

Alternative regimens for BV

- Intravaginal metronidazole gel (0.75%) once a day for 5 days, or
- Intravaginal clindamycin cream (2%) once a day for 7 days, or

- Clindamycin 300 mg orally twice a day for 7 days.

Special situations

In pregnancy the safety of metronidazole is not established although the published data suggest no association with increased teratogenic risk^{13–15}. Metronidazole can be used in all stages of pregnancy and during breastfeeding, however high-dose regimens are best avoided in these circumstances.

In symptomatic TV infection in early pregnancy local therapies (clotrimazole pessaries 100 mg daily for 7 days or Aci-jel) could be used to provide symptomatic relief, but systemic therapy will ultimately be necessary to eradicate the infection.

There is no effective alternative to 5'-nitroimidazoles in patients with TV. In patients with true metronidazole allergy, desensitization has been described^{16,17}.

Oral anti-candidal preparations should be not used in pregnancy. Topical nystatin, which is a polyene, gives a cure rate of 70–90% for candida, but may be useful in women with an organism with reduced sensitivities to azole drugs. The dose as a pessary is 100 000 units, 1–2 pessaries nightly for 14 nights.

Severe or persistent candidiasis in an abnormal host e.g. diabetic, or infection caused by a less susceptible pathogen, e.g. *C. glabrata*, may require longer duration of therapy of either topical or oral azoles. Nystatin may have a role for the latter.

MANAGEMENT OF PARTNERS**Candida and BV**

Routine screening and treatment of male partner(s) is not indicated.

Trichomoniasis

Partners should be screened for STIs and treated for TV regardless of the results of their tests. In a male contact of TV, found to have 'non-specific urethritis' (NSU) on screening, it is reasonable to treat for TV initially and then repeat the urethral smear before making a diagnosis of NSU.

FOLLOW UP**BV**

Only in women with persistent symptoms. If treatment is prescribed in pregnancy to reduce the risk of preterm birth, a repeat test should be made after 1 month and further treatment offered in BV has recurred³.

TV

Should be undertaken if the patient remains symptomatic following treatment, or if symptoms recur.

Persistent/recurring symptoms, therapy

- Check compliance and exclude vomiting of metronidazole
- Check possibility of re-infection from new or untreated partners.

Patients who fail to respond to first course of treatment often respond to a repeat course of standard treatment. If this fails and above excluded, then consider a high vaginal swab (HVS) or empirical treatment with erythromycin or amoxicillin to reduce β -haemolytic streptococci before re-treating with metronidazole, as some organisms present in the vagina may interact and reduce effectiveness of metronidazole.

If persistent treatment failure, the likelihood is that the organism is one that has evolved with the capability to exist under aerobic conditions. In these situations there is no reliably effective treatment.

Candida

Only in women with persistent symptoms.

Recurring candidiasis, therapy

Definition is four or more symptomatic episodes per year:

- Document frequency, establish diagnosis and confirm by culture

- Exclude risk factors (e.g. diabetes, underlying immunodeficiency, corticosteroid use, frequent antibiotic use).

Ongoing trials are addressing optimal therapy in these individuals, which is not yet established. Current recommendations are for an initial induction regimen followed by a maintenance regimen, for instance fluconazole 100 mg weekly or topical clotrimazole 500 mg weekly, for 6 months^{1,4}.

APPENDIX**Syndromic management of vaginal discharge**

In situations where it is not possible to examine the patient and where there is no access to laboratory tests, the World Health Organization (WHO) has developed an algorithm for the management of vaginal discharge (see Figure 1)¹⁸. Occasionally, cervical infection caused by chlamydia or gonorrhoea may result in vaginal discharge. Cervicitis may have serious sequelae if left untreated. The signs and symptoms of cervical infections are non-specific, and it has been found that a risk assessment is a more accurate predictor of cervicitis.

The treatment for specific infections is as detailed in the individual guideline for that infection.

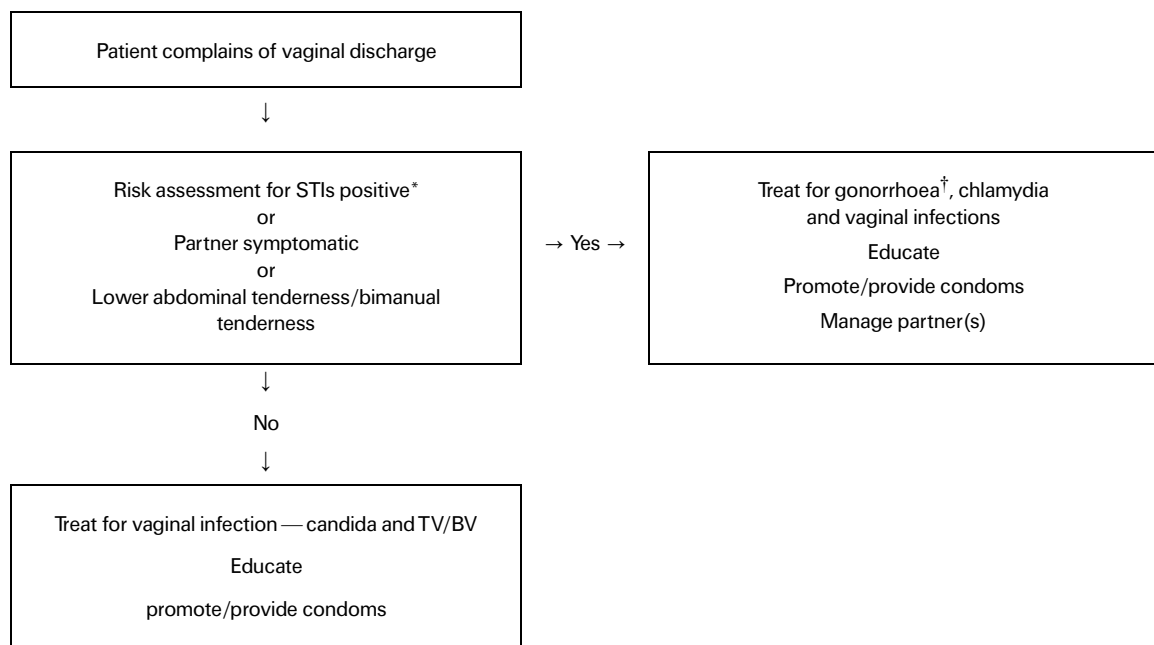


Figure 1. Algorithm for management of vaginal discharge. STI=sexually transmitted infection; TV=Trichomonas vaginalis; BV=bacterial vaginosis.

*Risk assessment for STIs. This will vary from area to area, but the WHO risk assessment is positive if any two of the following apply to the patient: age <21 years, single, more than one partner in last 3 months, new partner in last 3 months.

†Treatment for gonorrhoea. In some areas the prevalence of gonorrhoea is very low. Depending upon local epidemiological data it may be necessary to treat for gonorrhoea and chlamydia or chlamydia alone.

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MANAGEMENT OF SYNDROMES

European guideline for the management of tropical genito-ulcerative diseases

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INTRODUCTION

Chancroid, lymphogranuloma venereum and donovanosis are uncommon in Europe and the majority of cases are imports from developing countries. The correct identification of these pathogens causing genito-ulcerative disease (GUD) can usually be established if correct laboratory techniques are used to confirm the suspected diagnosis from the clinical impression.

CHANCROID

Introduction

- Causative pathogen: the gram-negative, facultative anaerobic bacillus *Haemophilus ducreyi*
- Chancroid is common in several areas of the world including Africa, the Caribbean and Southwest Asia. In Kenya, Gambia and Zimbabwe, chancroid is considered the most common cause of genital ulceration
- In European countries epidemics, generally limited, may occur, the source often being found in a commercial sex setting.

Diagnosis

Clinical

- Three days to 2 weeks after exposure to the pathogen, a small inflammatory papule or pustule arises at the site of inoculation. Within days, the lesion erodes to form an extremely painful, deep ulceration
- The characteristic ulcer is soft, friable, and non-indurated, with ragged undermined margins, a foul-smelling, yellow-grey exudative covering, and surrounding erythema. Several of these lesions may be present in one patient
- Within 1–2 weeks, painful inguinal lymphadenitis, most often unilateral, develops in 30–60% of patients
- This lymphadenitis progresses, in approximately 25% of patients, into a suppurative bubo, which may spontaneously rupture

- Autoinoculation may also occur resulting in classic opposing ulceration, known as 'kissing' lesions¹.

Laboratory

- Direct microscopy—various morphological forms of *H. ducreyi* have been described including 'schools of fish', 'railroad tracks' and 'fingerprints'². Although direct microscopy using a Gram stain allows rapid identification of *H. ducreyi* in some cases, it does not compare favourably with either culture or clinically diagnosed chancroid in most studies^{3–5}. Therefore, direct microscopy should not be relied upon for the final diagnosis of chancroid, although it may provide some information in some patients at the first visit⁶
- *In vitro* culture—although sensitivity may vary with different culture media, the *in vitro* culture remains the mainstay for the diagnosis of chancroid unless a DNA amplification test is available. Numerous media have been developed for culturing *H. ducreyi* and have been reviewed elsewhere⁷. Several authors have reported an increase in the sensitivity of culture by using combinations of media^{8–10}. Although using more than one culture medium increases the sensitivity of the culture, this is not a practical option at most sexually transmitted disease clinics
- DNA amplification methods—the sensitivity of polymerase chain reaction (PCR) techniques appears to be superior to bacterial culture. A number of primers have been developed to amplify specific sequences of either RNA or DNA of *H. ducreyi*². The sensitivity of *H. ducreyi* culture compared to DNA-PCR was approximately 75% in two studies that sampled genital swabs^{11,12}. To date, a commercially available PCR technique to detect *H. ducreyi* is unavailable. However, in view of superior sensitivity of PCR-based methods it can be expected that this technique will be available, as a replacement for, or an addition to, existing culture-based methods.

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Treatment^{1,13}

- Azithromycin 1 g orally (single-dose), or ceftriaxone 250 mg intramuscularly (IM) (single-dose)
- Erythromycin base/stearate 500 mg 4 times a day orally for 7 days
- Ciprofloxacin 500 mg twice a day for 3 days.

Worldwide, several isolates with intermediate resistance to either ciprofloxacin or erythromycin have been reported.

Special considerations

- Pregnancy—the safety of azithromycin for pregnant or lactating women has not been established. Ciprofloxacin is contraindicated in pregnant and lactating women, and in persons younger than 18 years-of-age. Thus, in pregnant and lactating women ceftriaxone or erythromycin should be preferred.

LYMPHOGRANULOMA VENEREUM (LGV)

Introduction

- Causative pathogen: *Chlamydia trachomatis* type L1, L2, L3
- Worldwide, LGV is an uncommon disease, thought to account for 2–10% of GUD in areas in India and Africa
- Men more often present with the acute form of LGV, whereas women more frequently present with complications of late disease
- Neither the degree of infectiousness nor the reservoir of disease has been proven, but transmission has been attributed largely to asymptomatic female carriers.

Diagnosis

Clinical

Disease course consists of three separate stages.

Following an incubation period of 3 to 30 days after inoculation, a small painless papule or pustule appears that may erode to form a small herpetic ulcer. This lesion usually heals within one week and often remains unnoticed by affected persons. At this stage, mucopurulent discharge may be present, affecting the urethra in men and the cervix in women.

The second stage begins within 2–6 weeks after onset of the primary lesion. It is commonly referred to as the inguinal stage and consists of painful inflammation and infection of the inguinal and/or femoral lymph nodes, LGV is primarily a disease of the lymphatic system that progresses to lymphangitis. The infected macrophages drain to the regional lymph nodes. Typically this produces unilateral enlargement, infection and abscesses. The painful lymph nodes are known as buboes, which may become fluctuant and rupture in one-third of patients. In other cases, they may develop

into hard, nonsuppurative masses. Although most buboes eventually heal without complications, some may progress into chronic sinuses. Approximately one-third of patients develop the ‘groove sign’, which results from enlargement of the inguinal nodes above and the femoral nodes below Poupart’s ligament. Inguinal lymphadenopathy occurs in 20% of women with LGV. Women more often have primary involvement of the rectum, vagina, cervix, or posterior urethra, which drain to the deep iliac or perirectal nodes. This may result in symptoms of lower abdominal pain or low back pain. Many women do not develop the characteristic inguinal lymphadenopathy; approximately one-third of them present with recognizable signs and symptoms of the second stage, whereas the majority of men present during this stage of disease.

Constitutional symptoms, such as low-grade fever, chills, malaise, myalgias and arthralgias, are often present during the second stage of disease. In addition, systemic spread of *C. trachomatis* occasionally results in arthritis, pneumonitis or (peri) hepatitis. Rare systemic complications include cardiac involvement, aseptic meningitis and ocular inflammatory disease.

The third stage of disease in LGV is often called the ‘genitoanorectal syndrome’ and is more often present in women. Patients initially develop proctocolitis followed by perirectal abscess, fistulas, strictures and stenosis of the rectum leading to ‘lymphorrhoids’ (similar to haemorrhoids). Without treatment, chronic lymphangitis leads to repetitive scarring and tissue repair resulting in strictures and fistulas of the involved region, which can ultimately lead to elephantiasis¹.

Laboratory

- Culture—a definite diagnosis of LGV can be made by isolating the organism from culture and cell typing of the isolate¹. Samples are best taken from an involved lymph node. A swab of the infected tissue may also be used. Bacterial culture of *C. trachomatis* L1, L2 and L3 remains a relatively insensitive technique. The sensitivity of bacterial culture does not reach above 50%, even if cyclohexamide-treated McCoy cells or diethylaminoethyl-treated HeLa cells are used^{14,15}
- Serology—diagnosis of LGV often rests on clinical presentation and serological testing, partly because *C. trachomatis* remains difficult to culture. High antibody titres are rapidly detectable because of the systemic nature of LGV. It is important to note that cross-reactions occur between different serotypes causing chlamydial infection. Nevertheless, with the appropriate clinical presentation, a complement fixation antibody titre of higher than 1:64 is considered diagnostic for LGV^{14,16}. In addition, a 4-fold increase in the complement

fixation titre of blood samples taken 2 weeks apart is indicative for LGV¹

- Alternative diagnostic laboratory methods—additional methods have been developed to detect *C. trachomatis* L1, L2 and L3. These include immunofluorescent testing with monoclonal antibodies^{17,18} and PCR-based techniques with or without analysing restriction fragment length polymorphism^{14,19}. These techniques are either not (yet) readily available, practical or sufficiently tested in large groups for routine use.

Treatment^{1,20}

- First choice—doxycycline 100 mg twice a day orally for 21 days
- Second choice—erythromycin 500 mg four times a day orally for 21 days.

DONOVANOSIS (GRANULOMA INGUINALE)

Introduction

- Causative pathogen; *Calymmatobacterium granulomatis* (*C. granulomatis*), a Gram-negative, facultative aerobic, obligate-intracellular, encapsulated bacillus
- Granuloma inguinale or donovanosis is endemic in certain tropical areas, such as Western Guinea, Southeast India, the Caribbean and adjacent areas of South America, Brazil, South Africa, and among aborigines in Australia.

Diagnosis

Clinical

- After an incubation period of 8 days to 12 weeks (median 2 weeks), single or multiple subcutaneous nodules or papules develop at the site of inoculation. These lesions enlarge and erode to form painless ulcerations with clean, friable bases and distinct, raised, rolled margins. Several lesions may become confluent resulting in local tissue destruction
- Autoinoculation is common producing lesions on adjacent skin, termed 'kissing' lesions
- Clinical morphological identification an diagnosis of donovanosis is difficult because of its pleomorphic presentation and atypical lesions
- The most common clinical variety of disease is the ulcerovegetative or ulcerogranulomatous form. This type produces large, extensive, nonindurated ulcerations with beefy-red, friable granulation tissue that bleeds easily
- The nodular variety consists of soft, red nodules or plaques, which erode to form ulcerations
- The hypertrophic or verrucous form consists of large, dry, vegetating masses that resemble condylomata acuminata

- The less common necrotic variant produces extensive and rapid destruction of tissue with profuse, grey, foul-smelling exudate
- The cicatricial or sclerotic form of disease is a rare form, which consists of dry, non-bleeding ulcers that expand into plaques with bandlike scarring. Lymphoedema often occurs in this variant
- Pseudobuboes may occur because of subcutaneous granulomas that arise superficially in the area of the inguinal lymph node.

Usually, donovanosis does not produce systemic symptoms. If these symptoms are observed it is suggestive for haematogenous dissemination, which may lead to death. Extra-genital sites may be involved by autoinoculation or extension into underlying organs, such as bone, bowel or bladder¹.

Laboratory

- Direct microscopy—the most practical and reliable technique to detect *C. granulomatis* still remains direct visualization of the bipolar-staining intracytoplasmic inclusion bodies called Donovan bodies. These pin-shaped structures can be detected within histiocytes of granulation tissue smears or biopsies from the affected site. Wright's stain or Giemsa's stain may be used, but silver stain is probably the most sensitive, particularly for specimens with sparse Donovan bodies²¹
- Culture— isolation of *C. granulomatis* is difficult and often impractical, but several reports have described successful isolation of this pathogen in a culture system²²⁻²⁴. These techniques are not available at the majority of (reference) laboratories
- Alternative diagnostic laboratory methods—a PCR-based technique for routine diagnosis of *C. granulomatis* has been reported²⁵. However, this test needs further validation using a sufficient number of samples from different geographical areas in order to ascertain its value for diagnosing donovanosis.

Treatment^{1,26}

- Co-trimoxazole 2 × 480 mg twice a day orally for 14 days
- Doxycycline 100 mg twice a day orally for 14 days
- Erythromycin base/stearate 500 mg four times a day orally for 2-4 weeks
- Azithromycin 1 g once a week orally for 4 weeks or 500 mg once daily for 7 days
- Gentamicin 1 mg/kg every 8 hours IM or IV.

Notes: Duration of treatment should be continued until all lesions have completely healed. Gentamicin is recommended as an adjunct to therapy in patients whose lesions do not respond in the first few days to

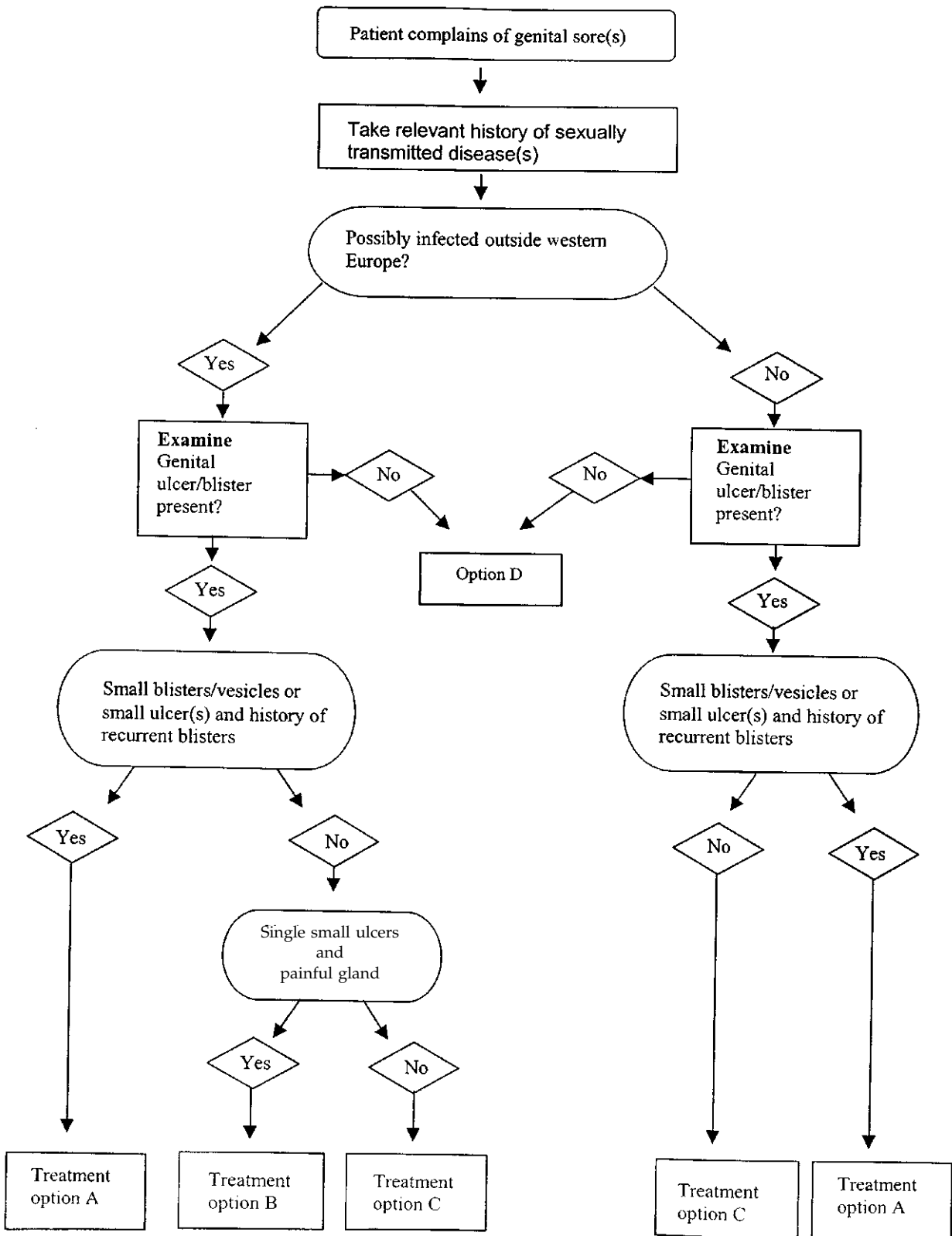


Figure 1. Syndromic management of genito-ulcerative diseases

other agents^{1,26}. In pregnant women erythromycin has been used successfully.

APPENDIX

Syndromic management of genito-ulcerative disease (GUD) (full diagnostic facilities unavailable)

Generally, in western European countries, laboratory facilities are available for screening and establishing the microbiological causes of GUD. However, such facilities may be unavailable. It is also possible that a patient with symptoms of GUD requires treatment before a confirmed diagnosis can be established. In such cases, the healthcare provider must rely on accurate history-taking and meticulous physical examination. The algorithm in Figure 1 provides a guideline for syndromic management of GUD, i.e. immediate treatment based on history and clinical examination at the first visit, which does not exclude collection of material for diagnostic tests. Similar algorithms have been provided by others and have been shown to be of practical value²⁷⁻³⁰.

In Figure 1, the treatment options A-D are as follows.

Treatment option A (treatment for genital herpes)

- Valaciclovir 500 mg orally twice daily for 5 days, or
- Famciclovir 250 mg orally 3 times a day for 5 days.

Treatment option B (treatment for early syphilis)

- Benzathine benzylpenicillin 2.4 million units IM (as the injections (1.2 million units in each buttock) can be painful, a lidocaine solution or another anaesthetic solution is often added to the penicillin solution), plus
- Treatment for lymphogranuloma venereum and chancroid: erythromycin base or stearate 500 mg 4 times a day orally for 2-4 weeks.

Treatment option C (treatment for early syphilis)

- Benzathine benzylpenicillin 2.4 million units IM, plus
- Treatment for chancroid:
 - Azithromycin 1000 mg orally, single dose, or
 - Ceftriaxone 250 mg intramuscular stat
 - Erythromycin base or stearate 500 mg 4 times a day orally for 7 days, or
 - Ciprofloxacin 500 mg orally twice a day for 3 days

Option D

- Counselling/education
- Promote/provide condoms.

Note: Saline baths can be useful in relieving complaints caused by GUD, especially in genital herpes lesions.

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MANAGEMENT OF SYNDROMES

European guideline for the management of pelvic inflammatory disease and perihepatitis

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INTRODUCTION

- Pelvic inflammatory disease (PID) is usually the result of infection ascending from the endocervix causing endometritis, salpingitis, parametritis, oophoritis, tubo-ovarian abscess and/or pelvic peritonitis
- *Neisseria gonorrhoeae* and *Chlamydia trachomatis* have been identified as causative agents^{1,2}, while *Gardnerella vaginalis*, anaerobes and other organisms commonly found in the vagina may also be implicated.

A number of factors are associated with PID:

- Young age
- Multiple partners
- Past history of STD (in the patient or their partner)
- Termination of pregnancy
- Insertion of intrauterine device within the past 6 weeks
- Hysterosalpingography
- *In vitro* fertilization procedure
- Post partum endometritis
- Bacterial vaginosis
- Recent new partner (within previous 3 months).

DIAGNOSIS

Clinical

PID may be symptomatic or asymptomatic. Even when present, clinical symptoms and signs lack sensitivity and specificity (the positive predictive value of a clinical diagnosis is 65–90% compared to laparoscopic diagnosis)^{1,3,4}.

The following symptoms are suggestive of a diagnosis of PID^{1,3–6}:

- Lower abdominal pain
- Dyspareunia
- Abnormal bleeding
- Abnormal vaginal or cervical discharge.

These signs are associated with PID:

- Lower abdominal tenderness

- Adnexal tenderness on bimanual vaginal examination
- Cervical motion tenderness on bimanual vaginal examination
- Fever (> 38°C).

The differential diagnosis of lower abdominal pain in a young woman includes:

- Ectopic pregnancy
- Acute appendicitis
- Endometriosis
- Complications of an ovarian cyst
- Functional pain (pain of unknown physical origin).

Indications for testing

PID should be considered in a patient with the clinical signs and/or symptoms outlined above or in an asymptomatic individual from a high-risk group (see Figure 1).

Laboratory

Testing for gonorrhoea and chlamydia in the lower genital tract is recommended since a positive result supports the diagnosis of PID. The absence of infection from the endocervix or urethra does not exclude PID^{1,3–5}.

- An elevated erythrocyte sedimentation rate (ESR) or C-reactive protein supports the diagnosis⁷
- Laparoscopy may strongly support a diagnosis of PID but is not justified routinely on the basis of cost and the potential difficulty in identifying mild intra-tubal inflammation or endometritis^{1,3,4}
- Endometrial biopsy and ultrasound scanning may also be helpful when there is diagnostic difficulty, but there is insufficient evidence to support their routine use at present.

MANAGEMENT

General

Broad-spectrum antibiotic therapy is required to cover *N. gonorrhoeae*, *C. trachomatis* and anaerobic infection^{1–3}. Evidence of long-term effectiveness in

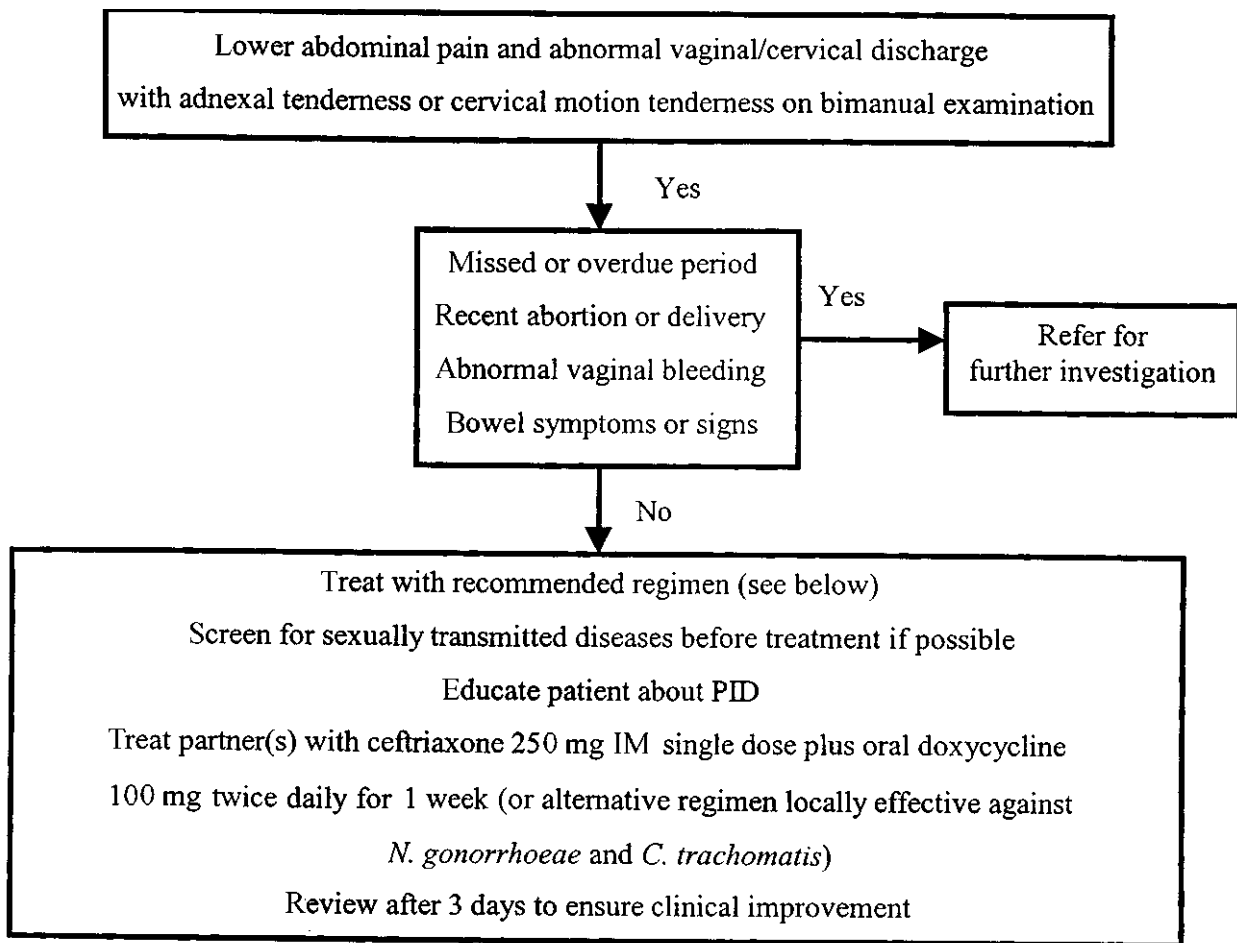


Figure 1. Syndromic management of pelvic inflammatory disease

preventing the complications of PID is currently lacking. There are comparatively fewer data on oral than parenteral regimens.

The choice of an appropriate treatment regimen may be influenced by:

- Robust evidence on local antimicrobial sensitivity patterns
- Robust evidence on the local epidemiology of specific infections in this setting
- Cost
- Patient preference and compliance
- Severity of disease.

General advice includes:

- Rest is advised for those with severe disease
- If there is a possibility that the patient could be pregnant, a pregnancy test should be performed
- Appropriate analgesia should be provided
- Intravenous (IV) therapy is recommended for patients with more severe clinical disease
- Patients should be advised to avoid unprotected intercourse until they, and their partner(s) have completed treatment and follow-up

- A detailed explanation of their condition with particular emphasis on the long-term implications for the health of themselves and their partner(s) should be provided, reinforced with clear and accurate written information.

Admission for parenteral therapy, observation, further investigation and/or possible surgical intervention should be considered in the following situations³:

- Diagnostic uncertainty
- Clinical failure with oral therapy
- Severe symptoms or signs
- Presence of a tubo-ovarian abscess
- Immunodeficiency
- Inability to tolerate an oral regimen
- Pregnancy.

All patients should be offered screening for sexually transmitted infections and HIV testing discussed.

Indications for therapy

It is likely that delaying treatment increases the risk of long-term sequelae such as ectopic pregnancy, infertility and pelvic pain^{3,5}. Because of this, and

the lack of definitive diagnostic criteria, a low threshold for empiric treatment of PID is recommended.

Recommended regimens

The following antibiotic regimens are evidence-based. Intravenous therapy should be continued until 24 hours after clinical improvement and then switched to oral. Dosage recommendations may need to be adjusted slightly depending on local licensing regulations and the availability of drug formulations.

Outpatient regimens

- Oral ofloxacin 400 mg twice daily *plus* oral metronidazole 500 mg twice daily for 14 days^{2,8-11}
- Intramuscular (IM) ceftriaxone 250 mg single dose *or* IM cefoxitin 2 g single dose with oral probenecid 1 g, *followed by* oral doxycycline 100 mg twice daily *plus* metronidazole 400 mg twice daily for 14 days^{2,3,8,9,12}.

Inpatient regimens

- IV cefoxitin 2 g four times daily (or IV cefotetan 2 g twice daily) *plus* IV doxycycline 100 mg twice daily (oral doxycycline may be used if tolerated), *followed by* oral doxycycline 100 mg twice daily *plus* oral metronidazole 400 mg twice daily for a total of 14 days^{2,3,8,9,12}
- IV clindamycin 900 mg three times daily *plus* IV gentamicin (2 mg/kg loading dose followed by 1.5 mg/kg three times daily [a single daily dose may be substituted]), *followed by either* oral clindamycin 450 mg four times daily *or* oral doxycycline 100 mg twice daily to complete 14 days *plus* oral metronidazole 400 mg twice daily to complete 14 days^{2,3,9,12}.

Alternative regimens

- IV ofloxacin 400 mg twice daily *plus* IV metronidazole 500 mg three times daily for 14 days^{3,8-11}
- IV ciprofloxacin 200 mg twice daily *plus* IV (or oral) doxycycline 100 mg twice daily *plus* IV metronidazole 500 mg three times daily^{3,8,13}.

Where the above regimens are not available antibiotic therapy should be given for 14 days and attempt to cover:

- *N. gonorrhoeae*, e.g. quinolones, cephalosporins, penicillin (if locally sensitive)
- *C. trachomatis*, e.g. tetracyclines, macrolides
- Anaerobic bacteria, e.g. metronidazole.

Special situations

- Women with HIV may have more severe symptoms associated with PID but respond well to antibiotic therapy¹⁴. Parenteral regimens are recommended

- The Fitz-Hugh–Curtis syndrome comprises right upper quadrant pain associated with perihepatitis which occurs in up to 10–20% of women with PID and may be the dominant symptom. Although laparoscopic division of hepatic adhesions has been performed, there is insufficient clinical trial evidence to make specific recommendations for treatment beyond those for PID
- In pregnancy PID is associated with an increase in both maternal and foetal morbidity, therefore parenteral therapy is advised although none of the suggested evidence-based regimens are of proven safety in this situation
- There is insufficient data from clinical trials to recommend a specific regimen for pregnant women with PID and empirical therapy with agents effective against gonorrhoea, chlamydia and anaerobic infections should be considered, taking into account local antibiotic sensitivity patterns (e.g. IV cefoxitin 2 g three times daily *plus* IV erythromycin 50 mg/kg continuous infusion, with the possible addition of IV metronidazole 500 mg three times daily)
- There is no evidence of the superiority of any one of the suggested regimens over the others. Therefore, patients known to be allergic to one of the suggested regimens should be treated with an alternative.

MANAGEMENT OF PARTNERS

- Current male partners of women with PID should be contacted and offered health advice and screening for gonorrhoea and chlamydia. Other recent sexual partners may also be offered screening—tracing of contacts within a 6-month period of onset of symptoms is recommended but this time-period may be influenced by the sexual history
- Partners should be advised to avoid intercourse until they and their partner have completed the treatment course
- Gonorrhoea diagnosed in the male partner should be treated appropriately and concurrently with the index patient
- Concurrent empirical treatment for chlamydia is recommended for all sexual contacts due to the variable sensitivity of currently available diagnostic tests
- If adequate screening for gonorrhoea and chlamydia in the sexual partner(s) is not possible, empirical therapy for gonorrhoea and chlamydia should be given.

Further review 4 weeks after therapy may be useful to ensure:

- Adequate clinical response to treatment
- Compliance with oral antibiotics
- Screening and treatment of sexual contacts.

Repeat testing for gonorrhoea after treatment is recommended in those initially found to be infected. Repeat testing for chlamydia may be appropriate in those in whom persisting symptoms, compliance with antibiotics and/or tracing of sexual contacts indicate the possibility of persisting or recurrent infection.

FOLLOW UP

Review at 72 hours is recommended³, particularly for those with a moderate or severe clinical presentation, and should show a substantial improvement in clinical symptoms and signs. Failure to do so suggests the need for further investigation, parenteral therapy and/or surgical intervention.

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MANAGEMENT OF SYNDROMES

European guideline for the management of epididymo-orchitis and syndromic management of acute scrotal swelling

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INTRODUCTION

- In men younger than 35 years-of-age epididymo-orchitis is most often caused by sexually transmitted pathogens such as *Chlamydia trachomatis* and *Neisseria gonorrhoeae*^{1–14}
- In men older than 35 years-of-age epididymo-orchitis is most often caused by non-sexually transmitted Gram-negative enteric organisms causing urinary tract infections^{1–14}. This may be associated with a history suggestive of bladder outflow obstruction
- There is cross-over between these groups and complete sexual history-taking is imperative^{1,5,9–11,13–14}
- Epididymo-orchitis caused by sexually transmitted enteric organisms also occurs in homosexual men who engage in insertive anal intercourse^{1,15–16}
- Gram-negative enteric organisms are more commonly the cause of epididymo-orchitis if recent instrumentation or catheterization has occurred^{1,17–20}
- Anatomical abnormalities of the urinary tract are common in the group infected with Gram-negative enteric organisms and further investigation of the urinary tract should be considered in all such patients but especially in those older than 50 years^{1,21}.

DIAGNOSIS

General

The presence of a sexually transmitted pathogen is frequently associated with a new sexual partner or more than one sexual partner in the recent past.

Clinical

Symptoms (these are usually unilateral)

- Testicular pain
- Scrotal swelling.

Symptoms of urethritis (this is often asymptomatic^{10,11,14}):

- Urethral discharge
- Dysuria
- Penile irritation.

Symptoms of bladder outflow obstruction may also be present.

Signs—on examination patients are usually found to have:

- Tenderness to palpation on the affected side
- Palpable swelling of the epididymis.

They may also have:

- Urethral discharge (this may only be present on urethral massage)
- Hydrocoele
- Erythema and/or oedema of the scrotum on the affected side
- Pyrexia.

Laboratory

The following investigations should be undertaken¹:

- Standard sexually transmitted disease (STD) examination as in guideline on non-gonococcal urethritis (NGU) to look for presence of urethritis and/or *N. gonorrhoeae* and/or *C. trachomatis*²²
- Either a urethral smear or a first-pass urine specimen can be used to detect urethritis by confirming an excess of polymorphonuclear leucocytes (PMNLs)
- In patients with urethritis, gram-negative intracellular diplococci should be looked for to exclude the diagnosis of gonorrhoea. This has a sensitivity of >90% for detecting gonococcal infection, in experienced hands
- A Gram-stained urethral smear containing ≥ 5 PMNL per high-power ($\times 1000$) microscopic field (averaged over 5 fields with greatest concentration of PMNLs), and/or
- The identification of ≥ 10 PMNL per high-power ($\times 1000$) microscopic field (averaged over 5 fields with greatest concentration of PMNLs) on a Gram-stained preparation from a first-passed urine (FPU) specimen

- The presence of an observable mucopurulent/purulent urethral discharge is also indicative of urethritis². However, this cannot reliably differentiate between gonococcal and NGU and the absence of such a discharge does not exclude urethritis
- A urethral culture for *N. gonorrhoeae*
- *C. trachomatis* should also be sought
- Urinalysis of the mid-stream urine (MSU) specimen, using a dipstick which contains leucocyte esterase and nitrites, in addition to blood protein and glucose. These dipsticks are an established screening test for bacterial urinary tract infections (UTI). However, they have not been assessed specifically in a STD clinic²³. The presence of blood in the MSU is usually the result of taking a urethral smear, and positive leucocyte esterase activity may reflect urethritis and not a UTI, indeed a positive leucocyte esterase test in the FPU specimen is indicative of urethritis, although this has a poor sensitivity^{2,24–26}). Thus the results of these for diagnosing a UTI should be viewed with scepticism. Nevertheless, a positive nitrite test is very specific although its sensitivity is only 40–80%²⁷
- MSU for microscopy and bacterial culture.

Consideration should be given to:

- Colour Doppler ultrasound is useful to help differentiate between epididymo-orchitis and torsion of the spermatic cord^{28–31}.

Differential diagnosis

- Torsion of the testis
- Epididymo-orchitis secondary to *N. gonorrhoeae* or NGU including *C. trachomatis*
- Epididymo-orchitis secondary to enteric organisms
- Testicular or epididymal tumour.

Torsion of the spermatic cord (testicular torsion) is the main differential diagnosis. It is a surgical emergency. It should be considered in all patients and should be excluded first as testicular salvage becomes decreasingly likely with time^{32,33}. Torsion is more likely if:

- The onset of pain is sudden
- The pain is severe
- Tests performed during the initial visit show neither the presence of a urethritis nor likely UTI
- The patient is younger than 20 years-of-age (the peak incidence is in adolescents), but it can occur at any age^{32,33}.

MANAGEMENT

General

- Empirical therapy should be given to all patients with epididymo-orchitis before micro-

biological results are available¹¹. The antibiotic regimen chosen should be determined in the light of the immediate tests as well as the age of the patient, the sexual history, any recent instrumentation or catheterization and any known urinary tract abnormalities in the patient

- Bed rest, scrotal elevation and support, and analgesics are recommended. Non-steroidal anti-inflammatory drugs may be helpful^{34,35}
- **If torsion is suspected an urgent urological opinion must be sought.**

Epididymo-orchitis secondary to *N. gonorrhoeae* or NGU including *C. trachomatis*

General advice

- See guideline on management of urethritis²².

Indications for therapy

- Symptoms and signs of epididymo-orchitis
- Urethritis detected
- UTI not suspected.

Recommended regimens

- Doxycycline 100 mg twice daily for 14 days^{7,15}
- Ofloxacin 200 mg twice daily for 14 days^{9,36,37}.

For epididymo-orchitis where gonococcal infection is suspected, either of the following in addition to doxycycline should be given:

- Ciprofloxacin 500 mg stat or ceftriaxone 250 mg intramuscularly.

Antibiotics used for gonorrhoea may need to be varied according to local knowledge of antibiotic sensitivities. If tetracycline resistance is common ofloxacin may be preferable.

Epididymo-orchitis secondary to enteric organism

General advice

The following should be discussed and clear written information provided:

- A detailed explanation of what epididymo-orchitis is and what causes it
- Side-effects of treatment and importance of complying fully with it and what to do if a dose is missed.

Indications for therapy

- symptoms and signs of epididymo-orchitis
- UTI strongly suspected.

Recommended regimens

- Ofloxacin 200 mg twice daily for 14 days
- Trimethoprim 200 mg twice daily for 14 days
- Antibiotics used may need to be varied according to local knowledge of antibiotic sensitivities.

Epididymo-orchitis of indeterminate aetiology

General advice

The following should be discussed and clear written information provided:

- A detailed explanation of what epididymo-orchitis is and what causes it and the difficulty in initially establishing the exact cause
- Side-effects of treatment and importance of complying fully with it and what to do if a dose is missed
- Advised to abstain from sexual intercourse until the microbiological results from the MSU specimen are available.

Indications for therapy

- Symptoms and signs of epididymo-orchitis
- Unable to differentiate between sexually transmitted pathogen or non-sexually transmitted enteric organism as the aetiological agent.

Recommended regimens

- Ofloxacin 200 mg twice daily for 14 days.

MANAGEMENT OF PARTNERS

All sexual partners at risk should be assessed and offered epidemiological treatment if:

- Epididymo-orchitis secondary to *N. gonorrhoeae* or NGU including *C. trachomatis* is diagnosed
- Epididymo-orchitis of indeterminate aetiology is diagnosed and the subsequent MSU specimen is negative
- This needs to be handled sensitively and the confidentiality of the index patient maintained. The duration of look-back is arbitrary as the incubation period of epididymo-orchitis is unknown; 3 months is suggested
- The treatment regimen used should be as detailed for uncomplicated *C. trachomatis* infection³⁸ and include treatment for uncomplicated gonorrhoea³⁹ if this is isolated from the index case
- If *C. trachomatis* or *N. gonorrhoeae* are detected it is particularly important to ensure that all sex partner(s) potentially at risk have been notified
- Details of all contacts should be obtained at the first visit. Consent should also be obtained to contact either the patient or his partners if tests for *C. trachomatis* or *N. gonorrhoeae* are found to be positive. This ensures that if the index patient does not reattend, he can be contacted and/or provider referral can be initiated for sexual contacts
- Contact(s) of men with chlamydial or gonococcal epididymo-orchitis should be treated regardless of results of microbiological investigations

- Concurrent treatment of the sexual partners of men with chlamydia-negative and/or gonococcal-negative epididymo-orchitis is recommended as it may result in improved response in some patients, and a possible reduction in female morbidity, since:

- No test is 100% sensitive for detecting *C. trachomatis* in men
- There is evidence that at least some men with 'chlamydia-negative' NGU have partners who are chlamydia-positive⁴⁰.

FOLLOW UP

If there is no improvement in the patient's condition after 3 days then the diagnosis should be reassessed and therapy re-evaluated. Reassessment is required if signs of swelling and tenderness persist after antimicrobial therapy is completed, although in some cases symptoms take longer than this to settle. Surgical assessment may be appropriate in these cases^{41,42}.

Differential diagnoses to consider in these circumstances include¹:

- Testicular ischaemia/infarction
- Initial diagnosis of infective aetiology, i.e. enteric organism versus STI, was wrong and patient was therefore treated incorrectly
- Enteric organism resistant to therapy with trimethoprim or ofloxacin
- Abscess formation and/or scrotal fixation
- Testicular or epididymal tumour
- Mumps epididymo-orchitis
- Tuberculous epididymitis
- Fungal epididymitis
- Gonococcal infection resistant to fluoroquinolones and tetracycline.

If epididymo-orchitis secondary to *N. gonorrhoeae* or NGU including *C. trachomatis* is diagnosed, the patient's follow-up in addition should include that as detailed in the guideline for urethritis, with a repeat examination for urethritis at 2 weeks²².

SYNDROMIC MANAGEMENT OF ACUTE SCROTAL SWELLING

The principal diagnoses are epididymo-orchitis, torsion, trauma and a testicular or epididymal tumour. Without recourse to diagnostic facilities it may be difficult to differentiate between these. Torsion of the spermatic cord (testicular torsion) is the main differential diagnosis. It is a surgical emergency. It should be considered in all patients and should be excluded first as testicular salvage becomes decreasingly likely with time. The flow-chart (Figure 1) details the syndromic management of this condition.

Of importance in the management is the syndromic detection of urethritis. If urethritis is detected the most likely aetiology is epididymo-orchitis secondary to *N. gonorrhoeae* or NGU including *C. trachomatis*.

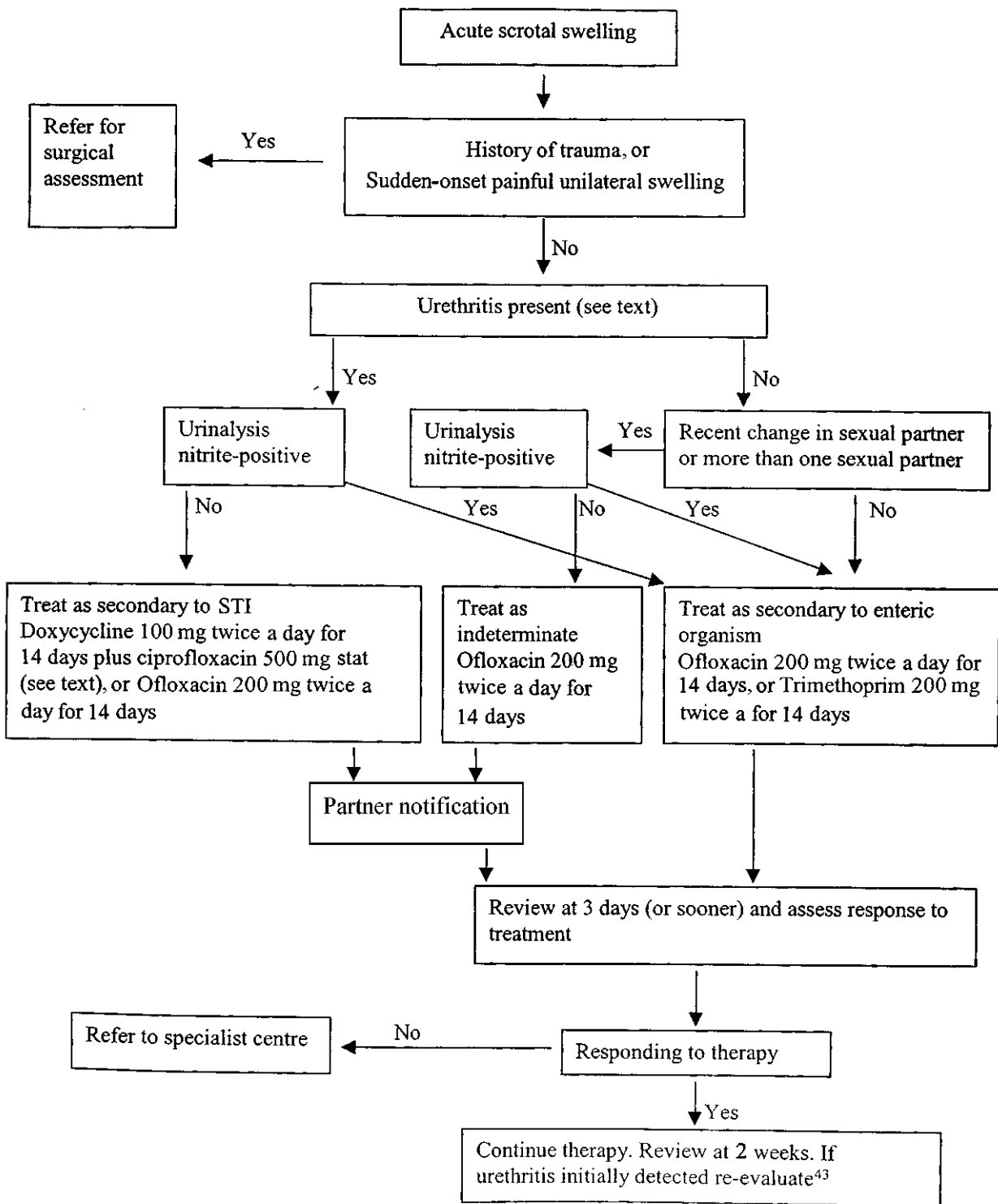


Figure 1. Syndromic management of acute scrotal swelling (see text)

How to do this is detailed in the guideline on the management of urethritis²² and summarized below. The use of urinary dipsticks containing nitrites, because of their specificity for detecting UTIs, would also be of clinical benefit (see above).

Diagnosis of urethritis—clinical

- Men should be examined for evidence of a urethral discharge. If none is seen, the urethra should be gently massaged from the ventral

part of the penis towards the meatus. This can be undertaken by the patient

- The absence of urethral discharge does not exclude urethritis
- In gonococcal infection the discharge is usually more evident and purulent than that in NGU. Nevertheless, the severity of urethritis cannot differentiate reliably between gonococcal and NGU.

Investigations

Microscope present:

- See guideline on urethritis²²
- Gram stain for Gram-negative diplococci to exclude gonorrhoea. This has a sensitivity of >90% in experienced hands.

Microscope absent:

- Mucopurulent or purulent discharge observable on examination, or
- Positive leucocyte esterase dipstick test on FPU specimen, or
- Positive two-glass urine test. The foreskin should be retracted fully and the patient asked to urinate into two clean specimen glasses, the first 10–20 ml into one glass, the rest into the second. If the urine is hazy, add sufficient 5% acetic acid to dissolve the phosphate crystals which are responsible for the haze. When there is infection of the anterior urethra, the haze will persist in the first glass of urine due to the presence of pus cells, threads or flecks, but the second will be clear. If both glasses are abnormal, the infection also involves the posterior urethra, bladder or kidneys. This is most likely to indicate a bacterial urinary tract infection but may also represent severe urethritis often due to gonorrhoea or may simply be due to the patient forgetting to void into two glasses and dividing the first glass into two.

Both the leucocyte esterase dipstick test and the two-glass urine test have reduced sensitivities compared to microscopy for detecting urethritis and are not recommended for the confirmation of NGU if microscopy is available.

Management

This is set out in the flow-chart (Figure 1). If microscopy has been used to diagnose urethritis, and this has been undertaken by an experienced operator, ciprofloxacin 500 mg can be omitted from the regimen: 'doxycycline 100 mg twice daily (BD) for 14 days plus ciprofloxacin 500 mg stat', as detailed for treatment of epididymo-orchitis as secondary to STI. Resistant gonococcal infection is likely to be more of a problem in countries where syndromic STI management guidelines are widely

used⁴³. Alternatives to ciprofloxacin 500 mg are detailed elsewhere^{22,39}.

Follow-up should take place after 3 days or sooner if there is no improvement. It is an essential part of management. The differential diagnoses for patients who fail to respond to therapy is as detailed previously. However, resistant gonococcal infection may be more common as a cause of failure, for the reason detailed above.

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European guideline for the management of sexually acquired reactive arthritis

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INTRODUCTION

Reactive arthritis (RA) is a sterile inflammation of the synovial membrane, tendons and fascia triggered by an infection at a distant site, usually gastrointestinal or genital. RA triggered by a sexually transmitted infection (STI) is referred to as sexually acquired reactive arthritis (SARA). This includes sexually acquired Reiter's syndrome, described as the triad of urethritis, arthritis and conjunctivitis, with or without other cutaneous or mucous membrane lesions, such as keratoderma blennorrhagica, circinate balanitis/vulvitis, uveitis, oral ulceration, cardiac or neurological involvement.

Most commonly lower genital tract infections, either urethritis or cervicitis, are associated with SARA, with objective features of SARA being present in 0.8–4% of cases^{1–3}. The place of upper genital tract infection, such as prostatitis and salpingitis, is unresolved. There is no direct association between SARA and human immune deficiency virus (HIV) infection, despite earlier suggestions of a link^{4,5}.

The precise mechanisms linking infective agents with SARA are not clearly understood, so links with specific micro-organisms are partly speculative:

- *Chlamydia trachomatis*, the commonest identifiable cause of non-gonococcal urethritis (NGU), has been the micro-organism most strongly linked to SARA, being identified in 35–69% of cases, using non-nucleic acid amplification techniques^{2,6–9}
- *Neisseria gonorrhoeae* has been linked with up to 16% of cases, as distinct from its role in septic, gonococcal arthritis^{1,10–13}. The precise role of this micro-organism in relation to SARA remains unknown
- *Ureaplasma urealyticum* has been linked with a few cases and may be a cause of SARA in a minority^{14,15}

- A causal role for other genital tract pathogens and commensals is possible, but there is currently insufficient evidence for evaluation.

Mechanisms of pathogenesis in SARA are unclear, although it appears to involve an immune response to uro-genital micro-organisms.

SARA appears to occur over 10 times more frequently in men compared to women, although under-recognition in women may be a problem^{1,13,16,17}. Possession of the HLA-B27 gene increases susceptibility to SARA by up to 50-fold^{2,7,11,16,18}.

DNA and/or surface antigens of *C. trachomatis*^{8,19–25}, *U. urealyticum*^{24,26} and other mycoplasmas²⁷ may be detected within joint material from individuals with SARA. It is possible that the persistence of viable micro-organisms intra-articularly is an important factor in the causation and perpetuation of the arthritis.

DIAGNOSIS

The diagnosis of SARA involves three major components, comprising evidence of genito-urinary infection, typical clinical features of spondyloarthropathy and extra-genital manifestations, and laboratory investigation.

Clinical, genito-urinary infection

- Sexual intercourse, usually with a new partner, within 3 months prior to the onset of arthritis^{2,7,16}
- A recent history of urethral discharge and/or dysuria in approximately 80% of men with SARA, although considerably fewer women are symptomatic^{7,9,12,13,16}
- Genital infection may be clinically manifest in men by urethritis, urethral discharge, dysuria and/or epididymo-orchitis and in women by muco-purulent cervicitis, with or without easily induced cervical bleeding, and/or abdominal pain. Infection may be asymptomatic, particularly in women^{7,9,12,13,16}
- Please refer to the relevant guidelines on urethritis, *C. trachomatis* and gonorrhoea.

Clinical, spondyloarthropathy and extra-genital manifestations

- Possible past or family history of spondyloarthritis or iritis^{1,12,17,18,28}
- Onset of first episode of arthritis within 30 days of sexual contact in 88% of patients, with a mean interval of 14 days between the onset of genital tract symptoms and arthritis^{1,2,12,16,17}
- Pain, with or without swelling and stiffness, almost invariably affecting 1–5 lower-limb joints in an asymmetrical distribution, especially at the knees and feet. Persistent small-joint involvement may be erosive. Upper-limb joint involvement is rare in the absence of psoriasis^{12,16–18}
- Enthesopathy—Pain and stiffness, with or without swelling at the sites of tendon or fascia attachments, especially the Achilles tendon and plantar fascia attachments to the calcaneum, which often results in difficulty in walking. Enthesitis and/or fasciitis occurs in approximately 20% of patients^{1,11,13,16,17}
- Tenosynovitis—Tenderness, with or without swelling over tendon sheaths with pain on movement and crepitus occurs in 30% and classical dactylitis may be seen in 16%^{16,17}
- Low back pain and stiffness is common in the acute episode and sacro-iliitis, with pain on direct sacral pressure, occurs in approximately 10% of patients during the acute episode, although care should be taken to distinguish it from lumbosacral disc disease or other pathology^{1,11–13,16,17,29,30}
- Irritable eyes, with or without redness, photophobia or a reduction in visual acuity—Conjunctivitis occurs in 20–50% of patients with SARA but iritis is less common occurring in around 2–11% of patients^{1,11–13,16,17,30}. Slit-lamp examination is necessary to differentiate between them. Rarely, corneal ulceration, keratitis and intra-ocular haemorrhage may be seen and optic neuritis and posterior uveitis have been described^{1,11,13,17}
- Psoriasiform rash which may be typical plaque or guttate cutaneous psoriasis in 12.5%¹², nail dystrophy in 6–12%^{12,30}, or typical psoriatic lesions of the glans penis or labia (circinate balanitis or vulvitis) in 14–40%^{1,11,13,16,17,30}, tongue (geographical tongue) in about 16%³⁰, or pustular psoriasis on the soles of the feet (keratoderma blennorrhagica) in up to 33%^{1,11–13,16,17,30}. The latter may rarely occur on the palms of the hands. Stomatitis and oral ulceration occur in approximately 10%^{11–13,17}
- Renal pathology, such as proteinuria, microhaematuria and aseptic pyuria, is seen in about 50% and is usually asymptomatic. Glomerulonephritis and IgA nephropathy rarely occur¹⁸
- Heart lesions are almost invariably asymptomatic although tachycardia and rarely pericarditis and aortic valve disease may occur.

Electrocardiographic abnormalities, including conduction delay, are recorded in 5–14% of patients^{11–13,17}

- Rare manifestations include thrombophlebitis of the lower limbs, subcutaneous nodules, nervous system involvement including meningococcal meningitis and nerve palsies^{1,12,13,17}
- Systemic symptoms of malaise, fatigue, weight loss and fever occur in approximately 10% of patients^{16,18–29}.

Laboratory

The following investigations are essential, often useful or sometimes useful^{6,11–13,16–18,28–31}.

Investigations which are essential

- Full screening for STIs, including *C. trachomatis* and *N. gonorrhoeae*
- Microscopic confirmation of urethritis in men by a Gram-stained urethral smear demonstrating ≥ 5 polymorphonuclear leucocytes (PMNLs) per high power ($\times 1000$) microscopic field, or ≥ 10 PMNLs per high power ($\times 1000$) microscopic field on a first-void urine sample
- Acute phase response tests such as, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), or plasma viscosity (PLV)
- Full blood count
- Urinalysis.

Investigations which are often useful

- Liver and kidney function tests
- HLA-B27
- X-rays of affected joints and sacro-iliac joints
- Electrocardiogram
- Echocardiogram
- Ophthalmic evaluation including slit-lamp assessment.

Investigations which are sometimes useful

- HIV antibody test
- Blood cultures
- Stool culture (if enteritic RA is suspected)
- Serology specific for *C. trachomatis*
- Synovial fluid analysis for cell count, Gram-stain, crystals, and culture
- Synovial biopsy
- Exclusion tests for other diseases with rheumatological features, for example, rheumatoid factor (rheumatoid arthritis), plasma urate (gout), chest X-ray and serum angiotensin-converting enzyme (ACE) level (sarcoidosis).

Prognosis

- In the majority of individuals with SARA the disease is self-limiting with a mean first-episode duration of 4–6 months^{1,16,17,30}. The complications of SARA are principally due to aggressive arthritis and are more likely if the individual possesses the HLA-B27 gene^{11,16}

- Approximately 50% have recurrent episodes at variable intervals^{1,12,17,28}
- Chronicity with symptoms persisting for more than one year occurs in approximately 17% of patients¹⁷
- Erosive joint damage especially affects the small joints of the feet with 12% exhibiting foot deformities, although severe deformity is rare¹
- Persistent locomotor disability occurs in approximately 15%, due principally to erosive damage with deformity of the metatarsophalangeal, ankle or knee joints, or as a consequence of sacro-iliitis or spondylitis^{11,28}. No accurate estimates of the prevalence of ankylosing spondylitis are available, although it has been described in up to 23% of patients with severe disease²⁹. It is unclear whether the development of ankylosing spondylitis is a complication of the RA or the independent development of two conditions in the same genetically predisposed population
- Inadequately treated, or recurrent, acute anterior uveitis may lead rapidly to cataract formation and blindness in a minority^{11-13,28}.

MANAGEMENT

General

- The principles of management are governed by the expectation that SARA is a self-limiting condition in the majority of patients
- Screening for STIs is essential and patients should be advised to avoid unprotected sexual intercourse until they and their partner(s) have completed treatment and follow up for any genital infection identified, or where epidemiological treatment is required
- Treatment is directed at several distinct elements of the condition and dermatovenereologists are advised to liaise with and/or refer to other relevant specialists, including rheumatologists and ophthalmologists, for all patients with significant involvement of extra-genital systems outside their areas of expertise. In particular, it is advised that all patients with SARA are referred to an ophthalmologist, if possible, for slit-lamp assessment
- Patients should be given a detailed explanation of their condition with particular emphasis on the long-term implications for the health of themselves and their partner(s). This should be reinforced by giving them clear and accurate written information.

Constitutional symptoms

- Rest
- Non-steroidal anti-inflammatory drugs (NSAIDs).

Genital infection

Antimicrobial therapy for any genital infection identified should be as in uncomplicated infection. Please refer to the relevant infection guidelines. Whether short-course antibiotic treatment of the acute genital infection influences the non-genital aspects of SARA is controversial, with the probability being that it does not once the arthritis is manifest^{16,30,32-34}.

Arthritis

For summary of treatment see Figure 1.

First-line therapy

- Rest with the restriction of physical activity, especially weight-bearing activity where leg joints are involved. Balance with the use of physiotherapy to prevent muscle wasting^{18,35-37}
- Physical therapy with the use of cold pads to alleviate joint pain and oedema^{18,35-37}
- NSAIDs are well established as efficacious agents in many inflammatory arthritides and form the mainstay of therapeutic management. It is important that they are used regularly to achieve the maximum anti-inflammatory effect. There is no definite drug of choice^{18,35-40}
- Intra-articular corticosteroid injections, especially valuable for single troublesome joints. May also be used for inflamed sacro-iliac joints. Proven value in other inflammatory arthritides but there are no-randomized placebo-controlled trials (RPCTs) of its use in SARA^{18,35,37,41-44}.

Second-line therapy (moderate/severe arthritis/failure of first-line)

As above plus:

- Systemic corticosteroids. If used, consideration should be given to anti-osteoporosis prophylaxis. Corticosteroids are valuable as short courses, usually beginning with oral doses of 10-25 mg daily, where severe symptoms arise from several joints, often in the presence of constitutional illness. In rheumatoid arthritis it has been shown to suppress inflammation but there are no RPCTs of its use in SARA^{18,35,45-47}
- Sulphasalazine. Indicated where disabling symptoms persist for 3 or more months, or evidence of erosive joint damage is present. Its effect is maximum on peripheral articular manifestations. Sulphasalazine reduces the duration of active synovitis but probably does not influence ultimate recovery. High doses (3g daily) are associated with significant toxicity, especially gastrointestinal, which

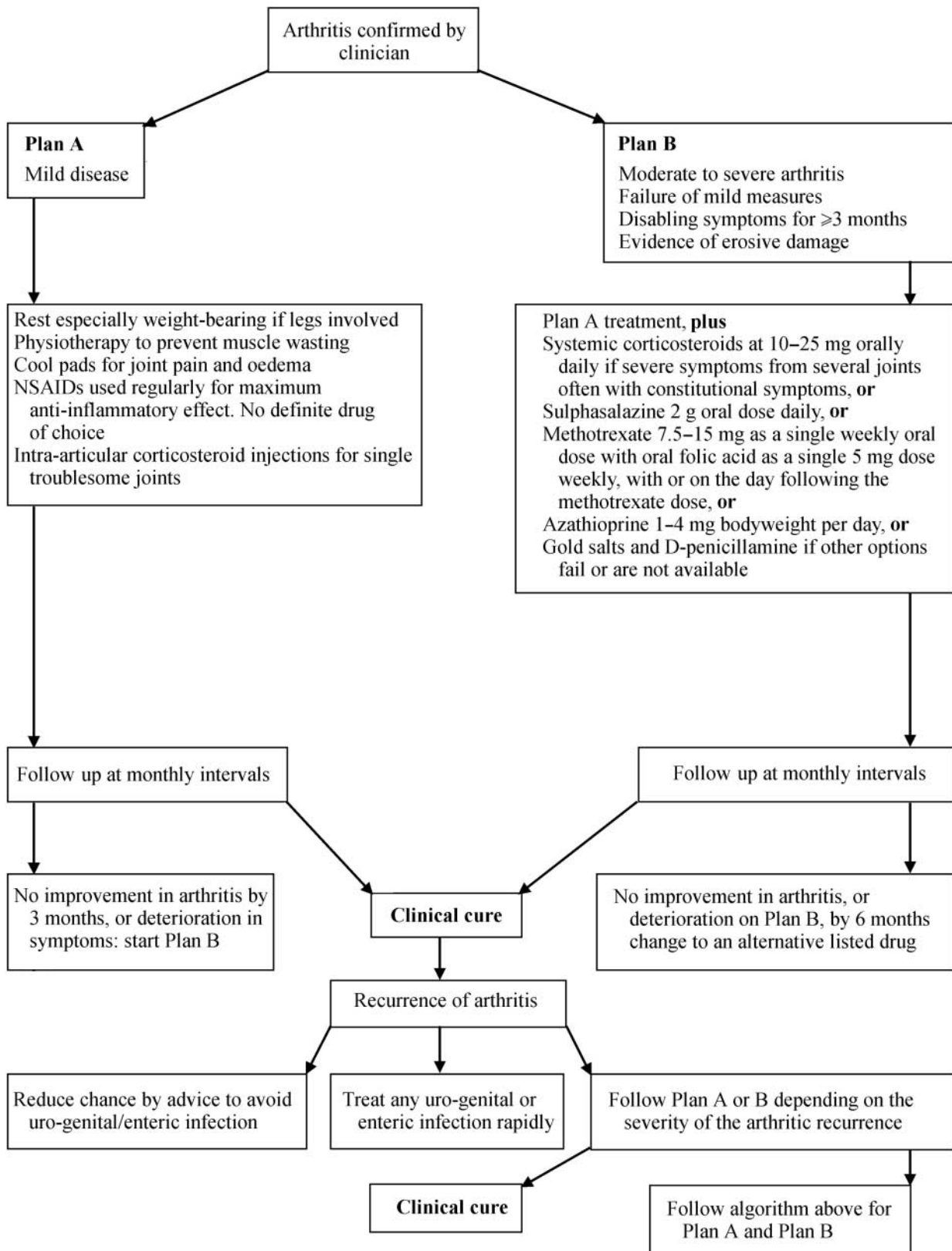


Figure 1. Management of arthropathy in sexually acquired arthritis. NSAID=non-steroidal anti-inflammatory drug

may necessitate cessation of treatment, whereas 2g daily appears equally effective and better tolerated^{18,35,48-51}

- Methotrexate. Indicated where disabling symptoms persist for 3 or more months, or evidence of erosive joint damage is present. Doses range from 7.5–15 mg orally as a single weekly dose. Oral folic acid should be given, usually as a single 5 mg dose weekly, with or on the day following the methotrexate dose. Methotrexate is favoured by many physicians because of the ease of weekly oral administration and the favourable responses seen in rheumatoid disease and psoriatic arthritis. Only case reports of its use in SARA have been published^{18,35,36,52}
- Azathioprine. Indicated where disabling symptoms persist for 3 or more months, or evidence of erosive joint damage is present. Doses of 1–4 mg/kg/body weight per day may be used^{18,35,53}
- Gold salts and D-penicillamine. These drugs are occasionally used when persistent poly-arthritis is present. No RPCTs have been published concerning their use in SARA^{18,35}
- Antibiotics. Short-course antibiotic therapy used for the treatment of concomitant uro-genital infection may reduce the risk of recurrent arthritis developing in individuals with a history of RA but otherwise there is little evidence of benefit in respect of arthritis^{16,30,32-34}. Longer-course antibiotic therapy has been considered. However, many studies have had small numbers of individuals with SARA, often the trial antibiotic has been ciprofloxacin a drug with low efficacy against *C. trachomatis*, and in the main antibiotic therapy has been commenced after the arthritis has established. Antibiotics may also have anticollagenolytic properties⁵⁴. Conflicting results have been obtained, with one study identifying a non-significant improvement in SARA with 3 months' treatment with ciprofloxacin compared to placebo, albeit with a diminishing effect after 12 months while others have identified no benefit⁵⁵⁻⁵⁷. Lyme cycline administered for 3 months, in one study, has been shown to reduce the duration of arthritis in *C. trachomatis*-triggered SARA, but no such effect was seen in a comparative study of 2 weeks versus 4 months of doxycycline therapy^{58,59}. The role of long-term antimicrobial therapy, particularly in non-chlamydial SARA, is not yet established^{33,55-61}
- Medical synovectomy using yttrium-90, osmic acid, or samarium-153. All have been shown to have short-term benefit in chronic mono-articular synovitis. Advantages over intra-articular corticosteroid injections have not been confirmed^{42,62}
- Surgery. Exceptionally, surgical treatment including synovectomy and arthroplasty, is valuable³⁵.

Enthesitis

For summary of treatment see Figure 2.

- Rest¹⁸
- Physiotherapy and ultrasound
- Orthoses, heel pads or cups for plantar fasciitis
- NSAIDs¹⁸
- Local corticosteroid injection^{37,42,43}
- Radiotherapy for persistent disabling heel pain, exceptionally
- Surgery, exceptionally.

Mucous membrane and skin lesions

For summary of treatment see Figure 3.

- No treatment for mild lesions
- Keratolytic agents, such as topical salicylate or corticosteroid preparations, in mild to moderate cases^{18,52}
- Calcipotriol cream/ointment in mild to moderate cases⁶³
- Methotrexate, if severe lesions^{18,52}
- Retinoids, such as acitretin, if severe lesions^{18,64}.

Eye lesions

- Should be managed with ophthalmology advice. Slit-lamp assessment is essential to diagnose uveitis, which if untreated may result

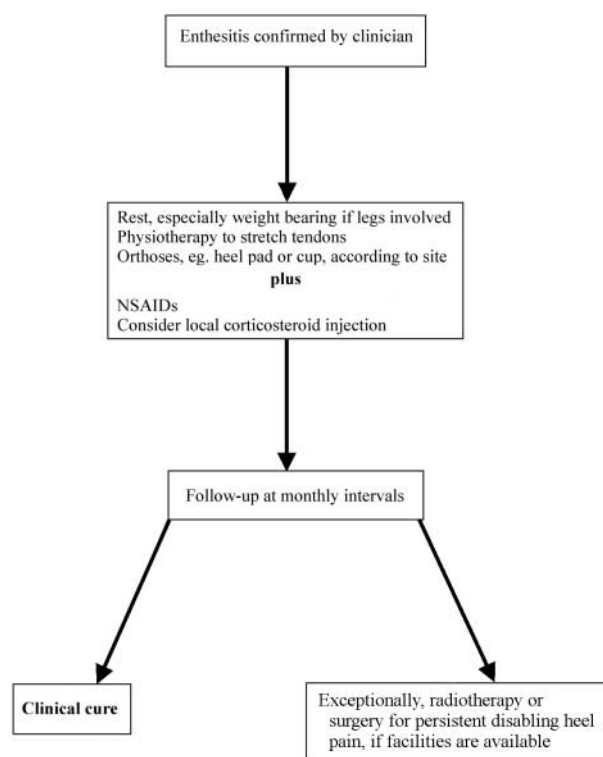


Figure 2. Management of enthesitis in sexually acquired reactive arthritis. NSAID=non-steroidal anti-inflammatory drug

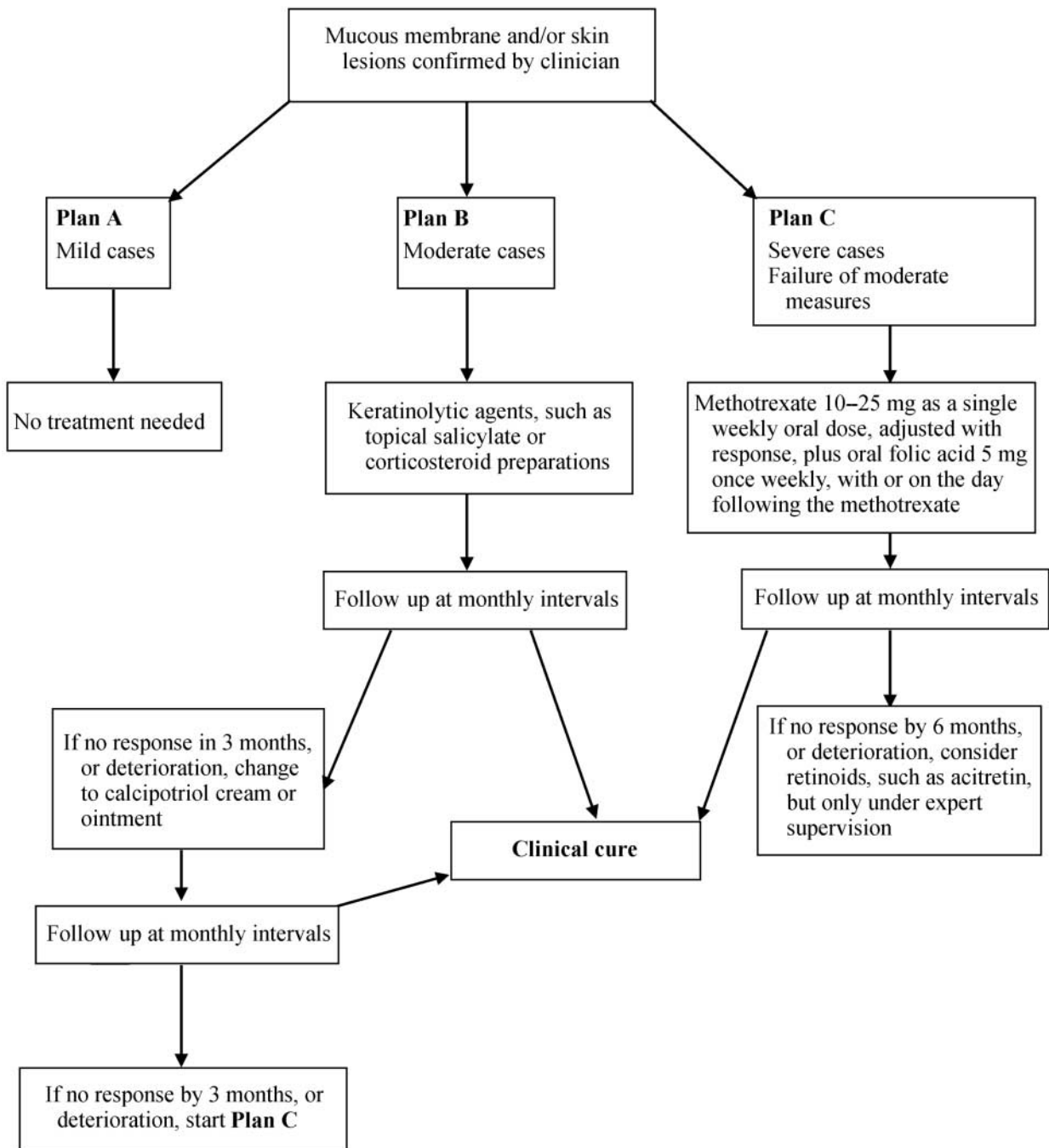


Figure 3. Management of mucous membrane and skin lesions in sexually acquired reactive arthritis

in irreversible visual loss. Therapy for uveitis consists of corticosteroid eye drops or oral corticosteroids, and mydriatics¹⁸.

Post-inflammatory pain and fatigue

- Explanation and patience
- Low-dose tricyclic drugs, such as amitriptyline 10–25 mg at night, if severe symptoms.

Special situations

Pregnancy and breastfeeding

- Avoid all medications during pregnancy and breastfeeding where possible
- Antibiotics. Please refer to the relevant infection guidelines
- NSAIDs may potentially produce sub-fertility as a result of the luteinized unruptured

ovarian follicle syndrome⁶⁵. NSAIDs, used regularly during pregnancy, may produce premature closure of the fetal ductus arteriosus, oligohydramnios, delayed onset and increased duration of labour^{66,67}. Advice regarding breastfeeding depends on the specific NSAID being used⁶⁷

- Corticosteroids are low-risk but prolonged or repeated systemic treatment increases the risk of intra-uterine growth retardation and fetal/infant adrenal suppression may occur. Systemic effects in the breastfeeding infant are unlikely, provided the maternal dose of prednisolone is less than 40 mg daily⁶⁷
- Sulphasalazine appears to have only small theoretical risks but should be used with caution in pregnancy and breastfeeding. It may induce oligospermia in men^{67,68}
- Azathioprine should not be initiated during pregnancy, if possible⁶⁷
- Methotrexate and retinoids are teratogenic and contraindicated during pregnancy and breastfeeding. Both men and women using methotrexate should avoid conception during drug-taking and for at least 6 months after. Women using retinoids, such as acitretin, should be advised to use adequate contraception for at least one month before treatment, during treatment, and for at least 2 years after stopping treatment⁶⁷
- Gold salts should be avoided during pregnancy and breastfeeding. Women should avoid conception during and for at least 6 months after treatment⁶⁷.

Prevention of recurrence

- Prevention of re-activation of SARA can be promoted by information concerning the avoidance of potential 'triggering infections' in the future, either uro-genital or enteric. Hence, safer sexual practice should be discussed and the importance of food hygiene explained.

MANAGEMENT OF PARTNERS

- Partner notification, treatment and the contact-tracing period is dependent on the genital infection identified. Please refer to the relevant infection guidelines.

FOLLOW UP

- Genitourinary medicine follow up is dependent on the genital infection identified. Please refer to the relevant infection guidelines
- Extra-genital manifestations should be followed up under the direction of the relevant specialist (see Figures 1–3)
- Parameters to be assessed include clinical symptoms and signs, the efficacy of treatment, microbiological and/or laboratory tests.

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