



ARTÍCULO DE REVISIÓN

CLINICAL PRACTICE GUIDELINE FOR SYNDROMIC MANAGEMENT OF PATIENTS WITH SEXUALLY TRANSMITTED INFECTIONS AND OTHER GENITAL TRACT INFECTIONS – 2013.

Guía de práctica clínica para el manejo sindrómico de los pacientes con infecciones de transmisión sexual y otras infecciones del tracto genital – 2013

Syndromic management of STI and other GTI guideline development group

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ABSTRACT

Objective: To reduce practice variability in the management of genital tract and sexually-transmitted infections (GTI/STI) and provide health care practitioners caring for GTI/STI patients with the most recent evidence regarding the effectiveness and safety of primary, secondary and tertiary prevention interventions alongside creating indicators for tracking the implementation of the guidelines and their impact on public health.

Materials and methods: A multidisciplinary development team was set up consisting of professionals in health care and patient representatives. Relevant clinical questions were posed and a search was made of the national and international guideline data-bases. Existing guidelines were evaluated for quality and applicability. None of the guidelines met the criteria for adaptation, therefore it was decided to develop *de novo* guidelines. The Pubmed, Ovid, Embase, Cochrane and Lilacs databases were searched for systematic reviews and meta-analyses, clinical trials and observational studies. Tables of evidence and recommendations were prepared using the GRADE approach based on informal and formal consensus methodology.

Results: The “Clinical Practice Guidelines” we reproduced, including recommendations and supporting evidence for prevention, diagnosis and treatment in terms of effectiveness and safety, and follow-up for cervicitis, urethritis, genital ulcers, vaginal discharge, scrotal inflammation and inguinal buboes.

Conclusions: The guideline’s core recommendation concerns patient management using a single dose and expedited patient treatment regarding sexual partners whenever possible. The guidelines must be updated in three years.

Key words: Clinical practice guidelines, sexually-transmitted infection, reproductive tract infection, cervicitis, urethritis, vaginal discharge, genital ulcer.

PROPOSAL AND SCOPE

The current guidelines are aimed at supporting clinicians/personnel providing health care for patients of both genders who may be susceptible to contracting/presenting sexually-transmitted infections (STI) and other genital tract infections (GTI). Genital tract infections arising from medical/surgical procedures were not included.

Recommendations were made for primary, secondary and tertiary health care levels. The primary level would involve prevention, risk assessment, early detection, and initial management and reference action. Secondary and tertiary levels would involve the management of STI/GTI complications as well as advice on preventing relapses or chronicity (secondary prevention). Managing specific conditions by sub-specialists recommendations are not covered within the scope of these guidelines.

The guidelines target the 14 to 74 year-old population residing in Colombia, regardless of a patient's health insurance scheme or whether a patient actually has health insurance.

As well as reducing variability regarding current practice in managing of GTI and STI, these guidelines are aimed at supporting health care personnel attending GTI/STI patients using the most recent evidence available regarding the effectiveness and safety of primary, secondary and tertiary prevention interventions. They also seek to cut the STI transmission chain, reduce the burden of disease associated with GTI/STI in Colombia and provide indicators for implementing such guidelines and for their impact on public health.

The syndromes accompanying genital tract conditions (the target for these guidelines) are the following:

1. Cervical infection syndrome (females).
2. Urethral discharge syndrome (males and females).
3. Genital ulcer syndrome (males and females).
4. Vaginal discharge syndrome (females).
5. Scrotal inflammation syndrome (males).
6. Inguinal bubo syndrome (males and females).

The guidelines for managing pelvic inflammatory disease/disorder (PID) will be published separately because it follows a different methodological adaptation (i.e. not *de novo* like the aforementioned syndromes). These clinical practice guidelines update the *Guidelines for Attending Sexually-Transmitted*

Diseases form an aging sexually-transmitted infections published in line with Colombian Ministry of Health Resolution 412 which proposed a syndromic approach to people suffering STI/GTI syndromes (1).

INTRODUCTION TO AND JUSTIFICATION FOR THE GUIDELINES

GTI are caused by microorganisms which are normally present in the reproductive tract or went it have been introduced for sexual contact or during medical-surgical procedures. They affect both females and males (2, 3). GTI not sexually transmitted are more common in females, particularly bacterial vaginosis (BV), a type of vaginal infection which is more common amongst reproductive aged females and which also represents the commonest cause of vaginal discharge, followed by *Candida albicans* (4, 5). STI are caused by different organisms: bacteria such as *Neisseria gonorrhoeae* and *Chlamydia trachomatis*, protozoa such as *Trichomonas vaginalis* and viruses such as *herpes simplex virus* (HSV), *human immune deficiency virus* (HIV) and *human papilloma virus* (HPV)(4).

GTI and STI frequently present with symptoms such increased vaginal secretion, urethral secretion, genital ulcers, pruritus, irritation, the presence of foetid odour or pelvic pain (6, 7). The signs and symptoms of infection have been grouped into the aforementioned clinical syndromes, following the supposition that they are caused by groups of specific organisms and that such grouping will lead to greater effectiveness in diagnosis and treatment. This should ideally occur during a patient's first contact with the health care services, especially when there is no access to laboratory services. The World Health Organisation (WHO) has recommended a syndromic management approach to treating STI and GTI (8).

The female syndromes proposed are vaginal discharge syndrome, which includes vaginitis caused by *Candida sp*, *Trichomonas vaginalis* and

bacterial vaginosis; the cervicitis syndrome mainly caused by *Neisseria gonorrhoeae*, *Chlamydia trachomatis* and finally pelvic inflammatory disease (PID) syndrome caused by *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, *Mycoplasma* (9) and anaerobic organisms gaining access to the upper genital tract (10). The scrotal inflammation syndrome caused by *Neisseria gonorrhoeae*, *Chlamydia trachomatis* and gram-negative bacteria (9) are proposed in males. Syndromes affecting both sexes include the genital ulcer syndrome caused by *Treponema pallidum*, *Haemophilus ducreyi*, *Chlamydia trachomatis* serotypes 1, 2 and 3, *Klebsiella granulomatis* and *Herpes simplex virus*, the inguinal bubo syndrome caused by *Chlamydia trachomatis* and *Haemophilus ducreyi* and the urethral discharge syndrome caused by *Neisseria gonorrhoeae*, *Chlamydia trachomatis* and *Trichomonas vaginalis* (9).

STI represent one of the main causes of morbidity in developing countries and carries a significant burden, both socially and financially to the country's health care system and its patients (11). A report dealing with STI in Colombia 1976-2000 concerned itself almost exclusively with the HIV/AIDS situation, reporting 406,722 years of potential life lost (YPLL) between 1991 and 1998 (12). The years of life lost and disability-adjusted life years (DALYs) due to STI (excluding HIV/AIDS) are secondary to the following complications: cancer (13), pelvic inflammatory disease (PID), pregnancy, infertility, chronic pelvic pain, complications of pregnancy such as ectopic pregnancy, chorioamnionitis or puerperal infection (11) and epididimitis and prostatitis in males (14). It is known that communities that have members who maintain an asymptomatic STI carrier state are associated with increased transmission and recurrence of community-acquired STI (11). Therefore greater importance should be given to identifying at-risk behaviour regarding STI transmission, alongside prevention, detection and management, including the treatment of sexual contacts/partners (8).

The available clinical practice guidelines for GTI/STI and their syndromic treatment will

provide health care administrators and professionals throughout Colombia with unified, evidence based, cost-effective tool to help guide optimal care of GTI/STI patients in all health care settings.

MATERIALS AND METHODS

The Guideline Development Group (GDG) consisted of experts in STI, clinical epidemiology, primary attention, urologists, infectologists, gynaecologists, psychologists, nurses, pharmacists, communicators and experts on the topics of public health and policy design. Patient's representatives were also included who gave their opinions during the different phases involved in developing the guidelines.

Once the clinical questions had been formulated, the GDG performed a systematic search of clinical practice guidelines (CPG) orientated towards identifying currently available national and international CPG. The systematic search for CPG was undertaken with the support of the Sexually transmitted infections Cochrane review group at the following sites: AHRQ-Clearing house, NHS, Guia Salud, Guidelines International Network, Scottish Intercollegiate Guidelines Network, National Institute for Clinical Excellence, Australian National Health and Medical Research Council, New Zealand Guidelines Group, World Health Organisation, Pan-American Health Organisation, TRIP database, Medline via PubMed, Lilacs via BVS (Biblioteca Virtual de la Salud). A search was also made of grey literature and the web pages of the various region's Ministries of Health via Google. The following terms were used in the search: Sexual* transmit* infection*; Sexual* transmit* disease*; Venereal*; STD*; enfermedades de transmisión sexual, using filters (Medline) "Practice Guideline"[ptyp] OR practice guideline*[tiab] OR guideline*[ti] OR recommendation*[ti] OR "Practice guidelines as topic" [MeSH].

The AGREE II instrument for evaluating the quality of the guidelines was utilised. The only guideline that was of relevance and fulfilled the quality criteria was that GPC for Pelvic inflammatory

Disease of the Royal College of Obstetricians and Gynaecologists (RCOG). Therefore, it was decided to adapt this CPG and develop *de novo* guidelines regarding the other aforementioned syndromes. A search of systematic reviews and meta-analyses from the last 10 years was performed with the support of Sexually transmitted infections Cochrane review group on Pubmed, Ovid, Embase, Cochrane Library and Lilacs databases. No articles were identified within this timeframe, so the timeframe was broadened. Systematic reviews were assessed for quality using the AMSTAR tool. For clinical questions that were not addressed by SRs, or where available SRs were of inadequate quality, a search of primary studies was performed, initially looking for clinical trials (CT), followed by cohort, cases and control and descriptive studies. These trials and studies were evaluated using the Scottish Intercollegiate

Guidelines Network (SIGN) tools. It was necessary to refer to recommendations made by other CPG for some topics (mainly low prevalence infections as the published evidence was extremely scarce). The evidence tables were prepared using GRADEpro software (version 3.6); the levels of evidence were rated according to GRADE classification (15) (Table 1).

Informal expert consensus was taken for preparing the recommendations. The GRADE method was used for preparing and rating the recommendations. The quality of the evidence, the risk-benefit balance, the costs and patients' preferences were also taken into account when doing this (16). The clinical questions for which recommendations could not be produced by informal consensus were submitted to experts formal consensus (Table 2)

Table 1. Levels of evidence according to GRADE methodology

Rating	Judgement	Characteristics
A	High ⊕ ⊕ ⊕ ⊕	It is highly unlikely that new studies will change the estimated result's confidence level
B	Moderate ⊕ ⊕ ⊕ ○	It is probable that new studies will have an important impact on the estimated result's confidence level and that these may modify the result
C	Low ⊕ ⊕ ○ ○	It is very probable that new studies will have an important impact on the estimated result's confidence level and that these may modify the result
D	Very low ⊕ ○ ○ ○	Any estimated result is very uncertain

Table 2. Degrees/strength of a particular recommendation following GRADE methodology

Recommendation strength	Meaning
Strongly in favour	The desirable consequences clearly exceed the undesirable consequences Definitely do it
Weakly in favour	The desirable consequences probably exceed the undesirable consequences Probably do it
Weakly against	The undesirable consequences probably exceed the desirable consequences Probably do not do it
Strongly against	The undesirable consequences clearly exceed the desirable consequences Definitely do not do it

GENERAL RECOMMENDATIONS

1. How should patients identified as being at highly likely of suffering from a GTI/STI be managed?

Strong recommendation in favour

A syndromic approach for the management of GTI/STI should be adopted. A diagnosis should be based on a combination of symptoms, signs and risk factors for acquiring an STI. Targeted treatment should be offered in the same initial consultation.

The effectiveness of syndromic management regarding an STI/GTI. Few clinical studies have evaluated the effectiveness of syndromic management of GTI/STI. A community-based randomised clinical trial has shown that a syndromic approach reduced the incidence of active syphilis (RR 0.58: 0.35–0.9695% IC) and the prevalence of infection caused by *N. Gonorrhoeae* (RR 0.28: 0.11–0.7095% IC) compared to other community strategies from an aging STI/GTI at population level (17). However, this was not statistically significant for *C. Trachomatis* infection (RR 0.99: 0.71–1.3995% CI). Grosskurth *et al.*, carried out a clinical study involving 8,845 patients, and found that syndromic management reduced the incidence of HIV (RR 0.58: 0.42–0.7995% IC) (18), however, a reduction in the incidence and prevalence of other STI was not observed. There were flaws in this particular study, including sample size and only being selective in males (level of evidence: moderate).

2. How should care be provided to a patient consulting due to symptoms of GTI/STI?

Strong recommendation in favour

Care should be provided individually in a private area, in a totally confi-

Strong recommendation in favour

dential setting. Plain language should be used throughout the consultation, which is neutral and non-judgemental. The clinical history should be elicited concerning the presence of symptoms such as external lesions, secretion from the urethra, vaginal discharge, bad smell, pruritus, rectal secretions, dysuria, abdominal pain or testicular pain. The presence of risk factors for STI must be ascertained, for example, irregular condom use, casual sexual relations, multiple sexual partners during the last six months, anal sex and sexual relations under the influence of alcohol or hallucinogenic drugs. A physical examination should be offered, searching for adenopathy (in particular inguinal nodes), fever and abdominal pain on palpation or rebound pain. In females, a pelvic examination should be undertaken to examine for vaginal discharge and the presence of ulcers and genital lesions on the labia minora and majora and anus. A speculum should be used to visualise the cervix, evaluate for the presence of endocervical secretions, assess the cervix for bleeding and examine the vaginal walls. Vaginal examination should be performed to detect pain or adnexal masses. In males, an examination of the penis, scrotum and anus should be performed alongside examining for the presence of urethral and anal secretions. The epididymis and testicles should be examined followed by a rectal examination in men who have had anal sex.

This recommendation was made by the group of national experts (level of evidence: very low)

3. Which are the most effective population strategies for preventing STI/GTI?

<i>Strong recommendation in favour</i>	Behavioural counselling should be provided for all sexually-active adolescents. It is recommended that the presence of risky sexual behaviour should be evaluated in adults when a patient consults due to GTI/STI symptoms, as well as during family planning consultation or prenatal care. Such counselling should include education regarding the GTI/STI syndrome they are presenting with, safe sexual practice and modifying unsafe practice.
<i>Strong recommendation in favour</i>	The use of latex or polyurethane condoms is recommended for preventing STI.
<i>Strong recommendation against</i>	The use of natural membrane condoms is not recommended for preventing STI.
<i>Strong recommendation against</i>	Nonoxinol-9 is not recommended for preventing STI.
<i>Strong recommendation against</i>	The use of spermicides containing nonoxinol-9 is not recommended for preventing STI.
<i>Strong recommendation against</i>	The use of non-barrier contraceptives are not recommended for preventing STI.
<i>Weak recommendation in favour</i>	Pharmacological treatment must be given to the sexual contacts of STI patients; Treatment must be chosen based on the organisms causing the suspected syndromes.
<i>Weak recommendation in favour</i>	Educational strategies for reducing risky sexual behaviour should be promoted as a useful tool aimed at reducing the prevalence of all STI.

Weak recommendation in favour

Education regarding abstinence is suggested as an effective strategy for reducing STI (particularly aimed at adolescents).

Counselling: Family planning consultations can be utilised as opportunities to explore sexual health risk taking behaviour in patients. Patients involved in high risk behaviours should be offered advice, information and an examination for STI. Advice should include strategies for reducing the risk of contracting STI, such as abstinence, using a condom, limiting the number of sexual partners, modifying sexual practice and vaccination. Counselling should be empathetic and unprejudiced. Such an approach should be adopted by all health care-related professionals; extensive training is not required as a prerequisite, but the quality of counselling improves when the provider has received some training and has developed the necessary inter-personal skills (4) (Level of evidence: very low).

Pre-exposure vaccination: Pre-exposure vaccination represents one of the most effective strategies for preventing the transmission of some STI. Two vaccines against VPH and one against *hepatitis B* are currently available. Vaccination strategies and schemes do not come within the scope of these guidelines; however, readers are invited to consult the respective Guideline (4).

Male condom: The male condom is highly effective in preventing STI when used consistently and correctly. However it has been demonstrated that using a condom as part of population policy for preventing STI does reduce the prevalence of syphilis, *Neisseria gonorrhoeae* and *Trichomonas vaginalis* (19). The failure rate of condoms for protecting against STI or unwanted pregnancy is likely secondary to its inconsistent or incorrect use, rather than it rupturing (4). The male condom is usually made of latex; other condoms are based

on polyurethane and other synthetic materials which provide effective protection against STI and unwanted pregnancy, having similar effectiveness to that of latex condoms (20). These condoms can be used by people who are allergic to latex. Natural membrane condoms made from animal tissue have 1,500 nm diameter pores which, in spite of not allowing sperm to pass, have a greater diameter than HIV and HBV, thereby allowing sexually-transmitted viral diseases to become acquired (20). Therefore use of natural membrane condoms is not recommended for preventing STI (4) (level of evidence: very low).

Female condom: Sexual partners should consider using a female condom when a male condom cannot be used correctly or consistently. The female condom can be used for protecting against STI during receptive anal relations (21) (level of evidence: very low).

Nonoxinol-9: A systematic review of the literature (22) evaluated the safety and effectiveness when compared to a placebo, of nonoxinol-9 (N-9) for preventing any type of sexually-transmitted disease (except HIV) in females. The review included ten controlled clinical trials (5,909 patients). The review had an AMSTAR score of 9/11. The meta-analysis had a low risk of bias but high heterogeneity. No statistically significant differences were found regarding the risk of acquiring infection due to *N. Gonorrhoeae* (RR 0.91: 0.67-1.2495% CI), cervicitis (RR 1.01: 0.84-1.2295% CI), *Trichomonas vaginalis* (RR 0.84: 0.69-1.0295% CI), *Chlamydia trachomatis* (RR 0.88: 0.77-1.0195% CI), BV (RR 0.88: 0.74-1.0495% CI) or *Candida sp.* (RR 0.97: 0.84-1.1295% CI). The females who were receiving N-9, compared to those receiving the placebo, had greater genital lesion frequency (RR 1.17: 1.02-1.3595% CI). There is evidence that N-9 does not protect against STI and that it could be harmful as it increases the genital ulcer rate; this product

cannot be recommended alone or in spermicides for preventing STI (level of evidence: moderate).

Contraceptive methods lacking a mechanical barrier do not provide protection against HIV and/or other STI. Sexually-active females using hormonal methods, an intrauterine device (IUD), who have undergone surgical sterilisation or have had a hysterectomy, should be counselled regarding the risk of acquiring STI and condom use. Genital hygiene methods such as vaginal douching and vaginal washing after unprotected sex are not effective in protecting against STI or HIV (4) (level of evidence: very low).

Treating a sexual partner: This refers to a continuum of activities designed to increase the number of infected people receiving treatment, aimed at interrupting the chain of infection transmission. There is limited evidence regarding the impact of notifying a sexual partner on the prevalence of these infections in the community (23). However, the probability of re-infection of the index/primary case is reduced, therefore health care providers must counsel patients on the importance of notifying their sexual partners and advise them on the need to seek medical evaluation and treatment (4). A systematic review (19) evaluated the effectiveness of mass treatment for STI in all members of a particular community, the distribution of contraceptives within the community, the syndromic management of STI and STI counselling. The review had an AMSTAR score of 9/11 and included four controlled clinical trials (57,000 patients). The review examined the reduction in the prevalence of STI, increasing health care service use, improving service quality and increasing safe sexual behaviour in the community, including condom use. It was found that the interventions significantly reduced the prevalence of syphilis (RR 0.88: 0.80-0.9695% CI), *N. Gonorrhoeae* (RR 0.49: 0.31-0.7795% CI) and trichomoniasis (RR 0.64: 0.54-0.7795% CI) but

not *C. trachomatis* (RR 1.03: 0.77-1.3695% CI). A significant increase was found regarding frequency of condom use (RR 1.18: 1.04-1.3395% CI) and frequency of consultation when seeking treatment for a STI (RR 1.22: 1.13-1.3295% CI) compared to control. The sole adverse effect was a small increase in the number of sexual partners (RR 1.07: 1.01 - 1.1395% CI) the included studies had a moderate risk of bias and were highly heterogeneous (level of evidence: moderate).

Educational interventions for adolescents regarding reducing the risk of HIV and sexually-transmitted diseases: A systematic review (AMSTAR score of 8/11) evaluated the effectiveness of two educational group strategies in adolescents applied within a scholastic or community setting. The two strategies were education strategy for reducing risky sexual behaviour (64 controlled clinical trials) and education regarding abstinence (23 controlled clinical trials). They focused on implementing counselling for preventing STI, distributing contraceptives, STI screening and carrying out educational campaigns aimed at reducing the prevalence of HIV and other sexually-transmitted disease. The included trials focused on educating adolescents in decision-making and practical skills, taking into account their attitudes and beliefs to aid effective communication. The education strategy for reducing risky sexual behaviour was significantly associated with reduced sexual activity (OR 0.81: 0.72-0.9095% CI), fewer sexual partners (OR 0.83: 0.74-0.9395% CI), fewer unprotected sexual contacts (OR 0.70: 0.60-0.8295% CI) and lower STI frequency (OR 0.65: 0.47-0.9095% CI). Regarding education concerning abstinence, the educational intervention was associated with less sexual activity (OR 0.81: 0.70-0.9495% CI), but there were no statistically significant differences regarding the number of sexual partners, the number of non-protected sexual contacts or condom use during sexual activity. This review did not make clear the

included studies risk of bias and there was high heterogeneity for some of the assessed outcomes (24) (level of evidence: moderate).

4. Which risk factors are associated with STI?

Certain socio-demographic characteristics and types of sexual behaviour increase the risk of contracting an STI. Several cohort studies and cases and control studies have reported risk factors for acquiring STIs. The following risk factors (Table 3) were taken into account, based on the studies reviewed here (25-45) alongside risk factors referred to by different CPG such as WHO 2005 (2), CDC 2010 (4) and Canadian CPG (9).

RECOMMENDATIONS FOR MANAGING SPECIFIC SYNDROMES

<i>Strong recommendation in favour</i>	A single dose treatment should be administered to patients presenting with an STI syndrome at the initial appointment, to ensure treatment is received as quickly as possible. When indicated, treatment should be sent to the sexual contact/partner.
<i>Weak recommendation in favour</i>	Sexual health consultations should be held in a suitable setting, where the same level of privacy and confidentiality to that of HIV counselling can take place. Diagnosis and treatment should be started on first contact with the patient.
<i>Strong recommendation in favour</i>	Expedited partner therapy (EPT) or treatment should be offered to the sexual contacts from the last 60 days, of patients who present with an STI. Consultation should be offered alongside treatment.
<i>Weak recommendation in favour</i>	It is suggested that EPT should be accompanied by an informative brochure about STI.

Table 3.
Risk factors related to sexually-transmitted infections

Sexually-transmitted infection	Risk factors
All STIs	<ol style="list-style-type: none"> 1. Sexual contact with people having a known STI 2. Sexual activity when aged less than 25 years old 3. Being an Afro-American 4. Having had more than two sexual partners during the last 12 months 5. Having a new sexual partner 6. Not using barrier contraceptives 7. Using alcohol or drugs 8. Having had previous sexually-transmitted diseases 9. Paid sex
Infection caused by syphilis	<ol style="list-style-type: none"> 1. Males having sex with males 2. Paid sex 3. Being over 30 years old
Venereal lymphogranuloma	<ol style="list-style-type: none"> 1. Males having sex with males
<i>C. trachomatis</i> and <i>N. gonorrhoeae</i>	<ol style="list-style-type: none"> 1. Being aged less than 25 years-old 2. Having had a previous gonorrhoeal infection 3. Other STIs 4. New or multiple sexual partners 5. Inconsistent condom use 6. Having paid sex 7. Drug use

Single dose: The recommendation regarding single dose treatment of STI syndromes, is based on the consensus of national experts. The recommendation is based on evidence supporting the use of azithromycin and ceftriaxone for the organisms mainly causing cervicitis, tinidazole and fluconazole for those causing vaginal discharge and penicillin G benzathine for syphilis in genital ulcer syndrome (level of evidence: very low).

Treating sexual contacts. A systematic review referring to the effectiveness of four strategies for notifying the partners of STI/GTI patients (10/11 AMSTAR score) included 26 RCT, involving 17,578 participants. The first strategy involved patients simply notifying their partners that they needed treatment (i.e. simple referral). If this method was accompanied by diagnostic leaflets or kits it was called “improved patient referral”. The second

strategy was expedited partner therapy (EPT) and consisted of sending treatment to the partner of a patient who had consulted, thereby avoiding the need for a doctor to examine the partner. A third strategy, involved health care provider referral, and consisted of information about the need for treatment being given by health care personnel. The fourth strategy was contract-based referral which involved a patient being responsible for communicating to their partner the need for treatment; however, when no response was obtained during a given time, the provider then contacted the patient. Regarding the number of partners treated per index patient, EPT was better than simple notification for patients suffering any STI syndrome (difference of means = 0.5: 0.34-0.6795% CI). No reliable evidence was found concerning the benefit of referral by provider or contract-based referral, nor was there evidence of an increase in adverse

events. There was a risk of selection bias due to problems in random assignment and a high risk of RCT performance bias arising from a lack of masking and more than 20% loss in 7 studies (46) (level of evidence: moderate).

The recommendation about sexual health consultation was agreed upon by the experts (level of evidence: very low).

CERVICAL INFECTION SYNDROME (CERVICITIS)

5. Which aetiological agents have been associated with cervical infection syndrome?

Managing cervical infection has been based on diagnosing and treating the main aetiological agents, these being *Chlamydia trachomatis* and *Neisseria gonorrhoeae* (4).

6. Which clinical manifestations of STI/GTI have been characterised for cervical infection syndrome?

According to the Canadian Guidelines form an aging STI, the signs and symptoms of cervical infection area mucopurulent discharge flowing from the cervix, cervical friability, strawberry cervix and vaginal discharge (9). Dyspareunia and dysuria represent other associated signs and symptoms (47). Syndromic management of cervical infection has been controversial as *Chlamydia trachomatis* infection is asymptomatic in 50 to 70% of reproductive-aged females (48); and its signs and symptoms do not have the desired operational characteristics, leading to a high proportion of false negatives. A sensitivity of 13.3 % has been found for the syndromic management of cervical infection. Vaginal discharge reported by a patient and found during clinical examination is the most sensitive sign for syndromic diagnosis (49.7% sensitivity, 78.3% specificity) (49).

Strong recommendation in favour

It is recommended that patients engaging in at least one risk type of sexual behaviour (such as irregular condom use, having casual sexual relations, multiple sexual partners during the last six months, anal sex, engaging in sexual relations under the effect of alcohol or hallucinogenic drugs) should have a rapid test for *C. trachomatis* and *N. gonorrhoeae*. Such rapid tests must be done on site, and at the same time as the initial consultation. A positive result is an indication for treatment for cervicitis syndrome.

It has been reported that the sensitivity of the rapid tests for *C. trachomatis* applied in health care settings varies from 17% to 49%; these tests specificity varies between 90% and 100% (50-53). However, a cost effectiveness study carried out in Colombia has shown that using rapid tests for *N. gonorrhoeae* and *C. trachomatis* represent the most cost-effective strategy for managing cervicitis when compared to syndromic diagnosis (54) (level of evidence: low).

7. Which is the most effective and safest treatment for cervical infection syndrome?

Strong recommendation in favour

A single oral dose of 1 g azithromycin plus a single intramuscular dose of 500 mg ceftriaxone should be given for the syndromic management of cervical infection patients

Strong recommendation in favour

A single oral dose of 1g azithromycin should be used as the first option for treating patients having suspected cervical infection or when *Chlamydia trachomatis* is confirmed. When azithromycin is not available or when

	<p>there are contraindications* to its use, then 100mg doxycycline orally every 12 hours for 7 days should be used as the second option.</p> <p>*Contraindications: known hypersensitivity to azithromycin, erythromycin and/or other macrolide antibiotics and in patients with previous hepatic damage due to any cause or secondary to azithromycin in use.</p>
Strong recommendation in favour	<p>A single dose of 500mg IM ceftriaxone should be used as first option for treating patients having suspected cervical infection caused by <i>Neisseria gonorrhoeae</i>. When ceftriaxone is not available or when there are contraindications* to its use, then a single oral dose of 400mg cefixime should be used as second option. In cases of possible crossed sensitivity to penicillin, a single dose of 2g intramuscular spectinomycin is recommended as third treatment option.</p> <p>*Contraindications: hypersensitivity to ceftriaxone. It must be used with caution in patients with a history of hypersensitivity to penicillin.</p>
Strong recommendation against	<p>A single oral dose of 500 mg ciprofloxacin is not recommended in managing patients suspected of being infected by <i>Neisseria gonorrhoeae</i> due to reports of bacterial resistance.</p>

Treatment of patients suffering *C. Trachomatis* infection: A meta-analysis (55) compared two treatments (azithromycin 1.0 g one dose versus doxycycline 100 mg every 12 hours for 7 days) evaluated 12 randomised clinical trials (RCT) involving 1,543 patients with urethral discharge or uterine cervicitis caused by *C.trachomatis*, (AMSTAR

score 7/11). It was rated as being of very low quality due to a lack of rigour regarding the searches for information and the indirect comparisons made in the population. The authors stated that the quality of the studies included was doubtful due to the small sample sizes and lack of blinding in more than half the studies included, as well as losses to follow-up being greater than 20%. The outcome was microbiological cure or negative culture for *C. trachomatis* in follow-up ranging from 2 to 5 weeks post-treatment. It was found that the percentage of patients having an aetiological diagnosis of genital infection caused by *C. Trachomatis* treated with azithromycin in whom microbiological cure was identified at the end of 3.7 weeks follow-up, on average did not significantly differ from the percentage of patients having the same outcome and who had been treated with doxycycline (96.5% and 97.9% microbiological cure, respectively, difference between proportions 0.0014: -0.007–0.02295% CI; Z=1.05; p=0.296). No differences were found regarding the presence of adverse effects in patients suffering genital infection caused by *C. Trachomatis* who had been treated with azithromycin (25%), compared to patients who had received treatment with doxycycline (22.9%; p = 0,533).

Three randomised clinical trials were published following the publication of a systematic review by Lau *et al.* The first of them was carried out by Sendağ *et al.*,(56); this study had serious methodological limitations (high risk of bias and imprecision). The study involved 131 females, 42 of them had a positive culture for some of the diseases being analysed (*Ureaplasma urealyticum*, *Chlamydia trachomatis*, *Mycoplasma hominis*). 71.4% of the females treated with azithromycin and 77.3% of those treated with doxycycline had negative cultures after 2 weeks of follow-up, such differences being reported as not being statistically significant. The authors offered no data for estimating association. Regarding syndromic management results, 42.9% of the females in the azithromycin group having a positive

culture (n=21) and 54.5% of the females from the doxycycline group having a positive culture (n=23) were found to be free of clinical signs of cervicitis at 2 weeks follow-up. The authors did not report association estimators, just outcome frequency. Another RCT was conducted by Guven *et al.*, (57) where the therapeutic effect of treatment with a single dose of 1 g azithromycin was compared to 100 mg doxycycline every 12 hours for 7 days in females who had consulted due to different symptoms (not clarified by the authors) and who were positive for *Chlamydia trachomatis*, *Ureaplasma urealyticum* and/or *Mycoplasma hominis* according to immunoenzyme assays. Only 81 of the 533 females initially studied were positive for some of the aforementioned STI. They were randomly assigned to each treatment (the authors did not report the method). The eradication rate was reported to be 87.3% and 93.5% in the azithromycin and doxycycline groups, respectively. A clinical trial by Rustomjee *et al.*, (58) evaluated the effectiveness of treatment with azithromycin (n=45) compared to treatment with doxycycline plus ciprofloxacin (n=37) for an aging cervicitis caused by *Chlamydia trachomatis* or *Neisseria gonorrhoeae*, diagnosed by clinical exam, immunoassay and endocervical gram staining. Twenty-six of the females studied were infected by *Chlamydia trachomatis*, 19 had *Chlamydia trachomatis* and *Neisseria gonorrhoeae* infection and 37 were infected by *Neisseria gonorrhoeae*. The patients from both groups were comparable, except for their age and the presence of trichomoniasis. The groups were analysed according to the aetiological agent isolated, so that microbiological cure was reported according to the bacteria and not according to the randomised groups. The percentage of microbiological cure in the groups infected by *Chlamydia trachomatis*, *Chlamydia trachomatis*, *Neisseria gonorrhoeae* and *Neisseria gonorrhoeae* using azithromycin was 100%, 90% and 100%, respectively; 100% cure was achieved in the three groups for the same infections regarding the doxycycline plus ciprofloxacin group. The authors did not report association measures. No statistically

significant differences were found regarding adverse event incidence (level of evidence: very low).

Treating patients suffering cervical infection caused by *Neisseria gonorrhoeae*: An RCT by Rehman *et al.*, (59) evaluated a microbiological cure for patients of both genders having signs and symptoms of urethritis or cervicitis who had a positive aetiological diagnosis for *Neisseria gonorrhoeae*; 300 patients aged 14 to 55 years old were studied: 229 females and 71 males. They were randomly assigned to one of three treatment groups: a single dose of 500 mg ciprofloxacin, 500 mg IV ceftriaxone or 2 g IM spectinomycin. Cure was determined by the absence of symptoms and Gram staining plus microscopy of prostatic fluid or vaginal secretion. Reported clinical efficacy was 90% in the ceftriaxone group, 94% in the spectinomycin group and 80% in the ciprofloxacin group. The authors only described proportions/percentages; they did not calculate measures of association (level of evidence: very low).

The CDC 2010 clinical practice guidelines (4) stated that ceftriaxone and cefixime were highly effective in treating urethritis and cervicitis caused by *Neisseria gonorrhoeae* and constituted the first-line treatment option. They also said that spectinomycin was an effective and useful treatment option for people who could not tolerate cephalosporins, however it is a costly, injectable drug which is not available in the USA therefore this antibiotic was not included in the CDC guidelines recommendations. However, other guidelines (i.e. Canadian 2008) recommended treatment with spectinomycin as an alternative drug to cephalosporins. The same guidelines did not recommend the use of ciprofloxacin for managing infections caused by *N. Gonorrhoeae* as this antibiotic is considered to induce resistance (9). The aforementioned two guidelines advised against using ciprofloxacin for infection caused by *N. gonorrhoeae* due to high bacterial resistance rates (level of evidence: very low).

8. Which complications are most frequently presented in cervical infection syndrome?

Ascend of the infection from the cervix to the upper genital tract causes complications as pelvic inflammatory disease (PID) which, in turn, can cause tubal infertility, ectopic pregnancy and chronic pelvic pain (60). The aetiological agents involved in developing cervicitis are also found in PID (*C.trachomatis*, *N.gonorrhoeae*, *Mycoplasma genitalium*) (61).

A prospective cohort study which assessed long-term follow-up for treatment of *C. Trachomatis* infection was examined. The study involved 443 females who had signs and symptoms of moderate to severe PID who had been followed-up for an average of 84 months. It was shown that these females had close to a 20% risk of developing PID within the following 3 years (HR 2.48:1.00- 6.27 95% CI). It was also shown that this risk was cumulative in relation to the number of infections caused by *C.trachomatis* (62). However, it has still not been possible to determine whether sequelae were due to bio-pathological mechanisms characteristic of the infection and/or whether they were attributable to limitations in the diagnosis (60).

9) Which type of follow-up is indicated for patients suffering from cervical infection syndrome?

<i>Weak recommendation in favour</i>	A clinical control is suggested 2 weeks after beginning treatment for patients suffering cervicitis.
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This recommendation emerged from expert consensus (level of evidence: very low).

10. How effective and/or safe is the treatment for the partner of a patient suffering cervical infection syndrome?

<i>Strong recommendation in favour</i>	Treatment consisting of a single oral dose of 1 g azithromycin plus a single oral dose of 400 mg cefixime should
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	be administered to the sexual partner or companion of patients suspected of having a cervical infection.
<i>Weak recommendation in favour</i>	Targeted treatment of the partner of a patient as a first-line option by administering treatment at the time of the initial consultation.
<i>Strong recommendation in favour</i>	EPT (Expedited partner therapy) is recommended for the sexual contacts made during the last 60 days, of patients suffering from cervicitis. This should be accompanied by consultation with the sexual contacts.
<i>Weak recommendation in favour</i>	It is suggested that EPT should be accompanied by an informative brochure about STI.

Treating *C. trachomatis* patients' partners.

A systematic review by Ferreira *et al.* (46), which analysed notification strategies, showed that EPT was better in urethritis or cervicitis patients than patient notification in terms of lower reinfection rates (6 RCT; RR = 0.71:0.56-0.89 95% IC; I₂ = 39%). No benefit was found when analysis was restricted to *C. trachomatis* (2 RCT; RR = 0.90: 0.60-1.35 95% IC; I₂ = 22%). Regarding the number of sexual contacts treated per index patient, EPT was better than simple reference in *C. trachomatis* or *N. Gonorrhoeae* infection patients (difference between means = 0.43: 0.28-0.58 95% IC). However, EPT was not better than improved simple notification using leaflets in preventing reinfection (3 RCT; RR = 0.96:0.60-1.53 95% IC; I² = 33%) (46) (level of evidence: moderate).

The CDC's 2010 CPG (4) recommended that if a patient is infected by *N. gonorrhoeae*, then he/she should also be treated for *C trachomatis*. Treatment should be accompanied by sexual and reproductive health education. This document states that if a patient is symptomatic and no more than 60 days have passed since the last sexual relation, then the partner should receive treatment. Furthermore, if they are treated, the patients must be told not to

have sexual contact until the treatment has been completed and the symptoms have disappeared (level of evidence: very low).

11. Which treatment is the most effective and safest for a pregnant or breastfeeding women suffering from cervical infection syndrome?

Strong recommendation in favour	A single oral dose of 1 g azithromycin plus a single oral dose of 400 mg cefixime should be used for the syndromic management of pregnant or breastfeeding patients suspected of cervical infection syndrome.
Strong recommendation in favour	A single oral dose of 1 g azithromycin should be used as first option for treating pregnant or breastfeeding women suspected of having cervical infection syndrome caused by <i>Chlamydia trachomatis</i> . 500 mg amoxicillin by oral route every 8 hours for 7 days should be used as second treatment option when azithromycin is not available or there are contraindications* to its use. *Contraindications: known hypersensitivity to azithromycin, erythromycin and/or other macrolide antibiotics; in patients having prior hepatic damage due to other causes and those associated with azithromycin use.
Strong recommendation in favour	A single oral dose of 400 mg cefixime should be used as first option for treating pregnant or breastfeeding women suspected of suffering cervical infection syndrome caused by <i>Neisseria gonorrhoeae</i> . When cefixime is not available or there are contraindications to its use then a single intramuscular dose of 125 mg

ceftriaxone should be used as second option. In case of suspected penicillin allergy, a single intramuscular dose of 2 g spectinomycin is recommended as third option.

Managing pregnant or breastfeeding women suspected as suffering or confirmed as having cervical infection caused by *Chlamydia trachomatis*: A systematic review by Brocklehurst (63) included 11 RCTs (1,449 females, AMSTAR score 10/11); comparing placebo or no treatment to antibiotic schemes in pregnant females suffering *C trachomatis* infection. The studies evaluated the microbiological cure and one neonatal adverse event. It was found that the treatment produced fewer microbiological failures compared to placebo or no treatment (OR 0.06:0.03–0.1295% IC). No statistically significant difference was found regarding the incidence of preterm birth (OR 0.89:0.51–1.5695% IC). Adverse events which required suspension of treatment were evaluated. The most frequently occurring adverse events were gastrointestinal (OR 4.83:0.60–38.6795% IC). Clindamycin and azithromycin appeared to be effective even though the studies sample sizes were small. Amoxicillin appeared to be equally effective as erythromycin regarding microbiological cure (OR 0.54:0.28–1.0295% IC). Clindamycin (600 mg threetimes aday for 10 days) appeared to be equally effective as erythromycin regarding microbiological cure (OR 0.40:0.13–1.1895% IC). A single dose of 1 g azithromycin appeared to be more effective than erythromycin regarding microbiological cure (OR 0.38:0.19–0.7495% IC). The estimation of effect showed risk of bias, indirectness and imprecision (level of evidence: low).

Managing pregnant or breastfeeding women suffering cervical infection (suspected or confirmed) caused by *Neisseria gonorrhoeae*: A systematic review by Brocklehurst (64) (9/11

AMSTAR score) which included 2 randomised clinical trials (346 patients), evaluated the maternal and neonatal morbidity of several treatment regimens for genital infection caused by *Neisseria gonorrhoeae* in pregnant women. The rates of failure of microbiological cure were similar in all treatment regimens: Amoxicillin plus probenecid versus spectinomycin (OR 2.29:0.74-7.0895% IC), ceftriaxone versus cefixime (OR 1.22:0.16-9.01 95% IC) and amoxicillin plus probenecid versus ceftriaxone (OR 2.29:0.74-7.08 95% IC). The author stated that the sample sizes were insufficient; therefore it is possible that the true effect regarding treatment effectiveness was not observed however he confirms the possibility of use ceftriaxone or cefixime in women with allergy to penicillin with a similar effectiveness regarding microbiological cure. Only one of the two studies included in the review (65) reported a case of treatment being suspended due to medication-associated adverse events. The reliability of the studies is affected by a high risk of bias and a high level of imprecision (very low level of evidence).

The CDC 2010 CPG (4) stated that all pregnant women from an area of high prevalence of *Neisseria gonorrhoeae* infection, should undergo routine screening for the infection at the first prenatal consultation. Women aged under 25 years of age, who have risk factors for *Neisseria gonorrhoeae* infection, should be screened again during the third trimester. Dual treatment for *Neisseria gonorrhoeae* and *Chlamydia trachomatis* was recommended, bearing co-infection in mind. The same document recommended administering a single IM dose 250 mg ceftriaxone alongside a single oral dose 400 mg cefixime and/or another single dose cephalosporin, accompanied by treatment with single dose oral 1 g azithromycin for infection caused by *Chlamydia trachomatis* (very low level of evidence).

12. Which complications present most frequently in pregnant females suffering from cervical infection syndrome?

Complications arising from *C. trachomatis* infection during pregnancy are related to the pathogen's vertical transmission when giving birth. If intra-partum infection occurs, the neonate could develop complications ranging conjunctivitis to pneumonia. A narrative review by Hammerschlag concluded that prenatal screening and antenatal treatment of cervical infection syndrome was effective for preventing gonococcal ophthalmia neonatorum and *C. Trachomatis* infection during the neonatal period (66) (level of evidence: very low).

13. How is persistent or recurrent cervical infection managed?

<i>Strong recommendation in favour</i>	An oral dose of 100 mg doxycycline every 12 hours for 7 days plus single intramuscular dose 500 mg ceftriaxone should be given for the syndromic management of women with suspected persistent or recurrent cervical infection.
<i>Strong recommendation in favour</i>	An oral dose of 100 mg doxycycline every 12 hours for 7 days should be given when treating women suspected or confirmed as having persistent or recurrent cervical infection syndrome secondary to <i>Chlamydia trachomatis</i> .
<i>Strong recommendation in favour</i>	A single intramuscular dose of 500 mg ceftriaxone should be given as first option for treating women suspected or confirmed as having persistent or recurrent cervical infection syndrome secondary to <i>Neisseria gonorrhoeae</i> . When ceftriaxone is not available or there are contraindications* a single intramuscular dose 2 g spectinomycin

should be used. *Contraindications: hypersensitivity to cephalosporins and in those with penicillin hypersensitivity as a precaution.

In cases of a second recurrence, a swab for culture and sensitivities for N. Gonorrhoeae should be performed to determine the resistance profile in regional reference public health laboratories.

Managing women suffering from persistent or recurrent cervical infection (suspected or confirmed) caused by *Chlamydia trachomatis*:

The group of experts has suggested the use of the doxycycline in cases of suspected recurrence. The treatment of partners, adherence to treatment and completing the course of treatment should be explored with women, alongside the importance of condom use with all sexual partners throughout treatment (Very low level of evidence).

Managing women suffering persistent or recurrent cervical infection (suspected or confirmed) caused by *Neisseria gonorrhoeae*:

The group of experts has suggested using Ceftriaxone in cases of suspected recurrence. The treatment of partners, adherence to treatment and completing the course of treatment should be explored with women, alongside the importance of condom use with all sexual partners throughout treatment. (Very low level of evidence).

URETHRAL DISCHARGE SYNDROME

14) Which aetiological agents are associated with urethral discharge syndrome?

N. gonorrhoeae, *C. trachomatis*, *Mycoplasma genitalium*, *Ureaplasma urea lyticum* and *Trichomonas vaginalis* are the pathogens most frequently responsible for urethral discharge syndrome (9).

15) Which clinical manifestations of STI/GTI are characterised by urethral discharge syndrome (UDS)?

The signs and symptoms characterising this syndrome are dysuria, irritation in the distal urethra or urinary meatus accompanied (sometimes) by erythema and urethral secretion (9). Initial syndromic management does not include laboratory tests.

16. Which treatment is the most effective and safest for Urethral Discharge Syndrome (UDS)?

Strong recommendation in favour

A single oral dose 1 g azithromycin plus a single intramuscular dose 500 mg ceftriaxone plus a single oral dose 2 g tinidazole should be used for the syndromic management of patients suspected of suffering UDS. When azithromycin is not available or there are contraindications* to its use, then oral 100 mg doxycycline every 12 hours for 7 days must be used. In cases when ceftriaxone is not available or there are contraindications** to its use, or in case of risk of crossed sensitivity to penicillin, then a single intramuscular dose 2 g spectinomycin must be used (very low level of evidence).

* Contraindications: known hypersensitivity to azithromycin, erythromycin and/or other macrolide antibiotics, and in patients with previous hepatic damage due to any cause or secondary to azithromycin use.***Contraindications: hypersensitivity to cephalosporins. It must be used with caution in patients with a history of hypersensitivity to penicillins.

Strong recommendation against

A single 500 mg dose of ciprofloxacin is not recommended for the management of patients suspected of *Neisseria gonorrhoeae* infection due to reports of bacterial resistance.

C. trachomatis infection: The evidence supporting the recommendation for treating *C. trachomatis* has already been described when answering the question about which is the safest and most effective treatment for cervical infection. A meta-analysis by Lau *et al.*, (55) compared two treatments (single dose 1 g azithromycin compared to 100 mg doxycycline every 12 hours for 7 days) for managing urethral discharge or cervicitis caused by *Chlamydia trachomatis*. There was no significant difference found between the microbiological cure rate of genital infection caused by *Chlamydia trachomatis* at an average of 3.7 weeks follow up, of patients who received azithromycin (96.5%) opposed to doxycycline (97.9%)(0.0014; -0.007-0.022 95% CI) (level of evidence: very low).

N. gonorrhoeae infection: The evidence supporting the recommendation for treating *N. gonorrhoeae* has already been described when answering the question about which is the safest and most effective treatment for cervical infection. An RCT which evaluated the microbiological cure rate of patients having signs and symptoms of urethritis due to *N. gonorrhoeae* was analysed. Patients were assigned to one of three treatment groups: single IM dose 500 mg ciprofloxacin, 500 mg ceftriaxone or 2 g spectinomycin. The percentage of patients diagnosed with urethritis or cervicitis caused by *N. gonorrhoeae* in which microbiological cure was identified after 5-day follow-up was 90% in the ceftriaxone group, 80% in the ciprofloxacin group and 94% in the group treated with spectinomycin (59). There was a high risk of bias and indirect evidence (level of evidence: very low).

17. Which complications are associated with Urethral Discharge Syndrome?

Urethritis in males can complicate acute epididymitis. Acute proctitis is frequently associated with venereal lymphogranuloma; however, there is no evidence concerning causal association between infection caused by *C. Trachomatis* and the development of prostatitis or male infertility (67). Reiter's syndrome (urethritis, conjunctivitis, arthritis and mucocutaneous lesions) as well reactive arthritis have been associated with genital infection caused by *C. trachomatis* (68) .

18. How should patients with Urethral Discharge Syndrome be followed up?

Weak recommendation in favour

A clinical control should be made for urethral discharge patients 2 weeks after beginning treatment.

This recommendation arose from expert consensus (level of evidence: very low).

19. How should the partner of a patient suffering Urethral Discharge Syndrome be treated?

Weak recommendation in favour

A single oral dose of 1 g azithromycin plus single oral dose of 400 mg cefixime plus a single oral dose of 2 g tinidazole should be used for treating sexual partners.

Weak recommendation in favour

Empirical treatment for sexual partners should be dispensed to give to their partners, or administered to the partner at the consultation depending on what is considered most suitable in each particular case.

Weak recommendation in favour

Expedited partner therapy (EPT) for sexual contacts made during the last 60 days of patients suffering urethral discharge is recommended

and a consultation should be arranged so that sexual contacts receive appropriate counselling and advice regarding STIs.

These recommendations have been based on indirect evidence regarding the effectiveness of treating partners of patients suffering cervical infection caused by *C. Trachomatis* and *N. Gonorrhoeae* (see the section dealing with cervicitis).

GENITAL ULCER SYNDROME

20. Which aetiological agents are associated with genital ulcer syndrome?

The agents responsible for genital ulcer syndrome (GUS) are *T. pallidum* causing syphilis, *H. ducreyi*, *C. Trachomatis* serotypes 1, 2 and 3, *Klebsiella granulomatis* and *Herpes simplex virus* (HSV) (9).

21. What are the clinical manifestations of genital ulcers?

GUS is characterised by ulcerative, pustular or vesicular genital lesions, often accompanied by regional lymphadenopathy. These lesions are located on the surface of the prepuce and the glans, scrotum, perineum and perianal region in men and the vulva, perineum, perianal region and the rest of the mucous surfaces (vagina and neck of the womb) in women (69). The characteristics of the ulcers is dependent upon the causative agent. In GUS caused by HSV infection, the ulcers develop following the rupture of vesicles or blisters and tend to be circular, erythematous and have diffuse edges and base. HSV often causes multiple small ulcers which might converge to form larger ulcers. The ulcers can be painful, and a patient could present with systemic symptoms of infection such as fever and inguinal lymphadenopathy. GUS secondary to primary syphilis often presents as a single ulcer or chancre, which characteristically appears round, firm, painless, has indurated borders

and a clean base and is possibly accompanied by lymphadenopathy. Alternatively, two or more painful necrotic ulcers can present in chancre related infections, accompanied by erythema and oedema in the surrounding area. The ulcer, which presents as a protuberance initially, may be accompanied by inguinal lymphadenopathy and abscesses called buboes. Venereal lymphogranuloma infection often presents with the signs and symptoms of urethritis, alongside single self-limiting papules followed by femoral lymphadenopathy, inguinal distension and/or proctocolitis. The clinical picture of inguinal granuloma infection presents with a single ulcerative lesion or multiple highly vascularised, non-painful ones which bleed easily on contact, located in 50% in the anal area. As time elapses, the initial protuberances become red nodules called granulation tissue which can extend to inguinal folds (4,9,69). It should be stressed that an initial syndromic approach to genital ulcers does not include laboratory tests.

Weak recommendation against

The use of rapid tests (point-to-care test) is not recommended for diagnosing primary syphilis infection in patients with genital ulcers (low level of evidence).

A systematic review of diagnostic tests which evaluated rapid test sensitivity and specificity for diagnosing syphilis in STI clinics and during the prenatal period estimated a mean sensitivity of 86% (IQR: 0.75-0.94) and a specificity of 99% (IQR:0.98-0.99). However, the included studies (13 cross-sectional studies) were focused on identifying any/all types of syphilis and thus test performance regarding primary syphilis could not be ascertained (70). No evidence was found referring to the tests operational characteristics or effectiveness for penicillin allergy concerning primary syphilis health care (level of evidence: low).

22. Which is the most effective and safest treatment for genital ulcer syndrome in females and males?

<i>Strong recommendation in favour</i>	<p>A single intramuscular dose of 2,400,000 IU penicillin G benzathine should be used for the syndromic management of genital ulcers when treating primary syphilis, plus a single oral dose of 1 g azithromycin (coverage for <i>H. ducreyi</i>). One of the following should be used in addition to the above treatment:</p> <ul style="list-style-type: none"> • When HSV infection is suspected, a 200 mg oral dose of acyclovir 5 times a day for 6 days should be added. • When venereal lymphogranuloma and inguinal granuloma infection is suspected then an oral dose of 1 g azithromycin should be added once a week for 3 weeks or oral 100 mg doxycycline, twice a day for 21 days.
<i>Strong recommendation in favour</i>	<p>A routine penicillin allergy test is not recommended; a detailed clinical history should be taken to establish if there is any background of systemic allergic reactions (type 1), such as angioneurotic o edema, generalised allergic reaction or respiratory difficulty. When such a history exists or if there are doubts about possible systemic reactions to penicillin, then this drug must not be administered; the suggested alternative medicament must be provided.</p>
<i>Strong recommendation in favour</i>	<p>The second line option of oral 100 mg doxycycline twice a day for 14 days should be adopted for patients suspected as having primary syphilis and for those with a history of penicillin allergy.</p>

<i>Weak recommendation in favour</i>	<p>The use of a single oral dose of 2 g azithromycin for treating primary syphilis is not recommended due to reports of bacterial resistance.</p>
<i>Weak recommendation in favour</i>	<p>Ceftriaxone use is not recommended for treating primary syphilis.</p>
<i>Strong recommendation in favour</i>	<p>A single oral dose of 1 g azithromycin should be used as the first line option for treating patients suspected of having <i>Haemophilus ducreyi</i> infection. When azithromycin is not available or there are contraindications to its use then a single intramuscular dose of 250 mg ceftriaxone should be used as the second line option. When ceftriaxone is not available, or there are contraindications to its use, then an oral dose of 500 mg erythromycin 3 times a day for 7 days should be used as a third line management option.</p>
<i>Strong recommendation in favour</i>	<p>Oral 1 g azithromycin once a week for 3 weeks should be used as first option for treating patients suspected of having venereal lymphogranuloma.</p>
<i>Strong recommendation in favour</i>	<p>Oral 100 mg doxycycline twice a day for 21 days should be used for treating patients suspected of having venereal lymphogranuloma and when azithromycin is not available or when there are contraindications to its use.</p>
<i>Strong recommendation in favour</i>	<p>The first line option for treating patients suspected of having inguinal granuloma should involve using an oral dose of 1 g azithromycin once a week for 3 weeks or until the lesions have been fully cured. When azithromycin is not available or there are contraindications to its use, then an oral dose of 100 mg doxycycline should be given twice a day for 3 weeks or until the lesions have been completely cured.</p>

<i>Strong recommendation in favour</i>	An oral dose of 200 mg acyclovir should be used 5 times a day for six days as the first line option for treating patients suspected of a first episode of genital infection caused by HSV type 1 or 2.
<i>Strong recommendation in favour</i>	An oral dose of 1 g valacyclovir twice a day for 7 to 10 days should be used as the second line option for treating patients suspected as suffering from a first episode of genital infection caused by HSV type 1 or 2 and when a cyclovir is not available.
<i>Strong recommendation in favour</i>	A dose of 200 mg acyclovir should be used 5 times a day for 6 days for patients suffering acute recurrent episodes of genital herpes.
<i>Strong recommendation in favour</i>	A dose of 500 mg valacyclovir should be used twice a day for three days in patients suffering acute recurrent episodes of genital herpes and when acyclovir is not available or when there are contraindications to its use. An oral dose of 400 mg acyclovir twice a day for 1 year should be used as prophylactic treatment for patients suspected of having recurrent genital herpes defined as having at least 6 episodes of herpes per year.
<i>Strong recommendation in favour</i>	When acyclovir is not available, an oral dose of 500 mg valacyclovir should be given twice a day for up to one year as the second line option.

Treating primary syphilis: The effectiveness of penicillin (in its different forms) has been established more by clinical experience than the availability of RCTs evaluating its usefulness. One RCT with 326 patients which brought together clinical experience of treating primary syphilis with penicillin, presented a high risk of bias related to follow-up, adherence to treatment and

co-interventions. The RCT included all types of syphilis as well as patients who had confirmed HIV. The results showed that patients diagnosed as having primary syphilis who were treated with penicillin G benzathine did not have a greater risk of failure of cure (confirmed by serology) compared to patients who had received additional treatment with amoxicillin and probenecid: 17.8 and 17.2% failure incidence, respectively (OR 1.11: 0.6–2.295% IC) (71)(level of evidence: very low).

Other options to penicillin have been studied, revealing a similar effectiveness profile. A meta-analysis which included four RCT and 476 patients (AMSTAR score 8/11) showed that patients diagnosed with primary syphilis who had been treated with azithromycin had a similar serological cure rate when compared to patients who were treated with penicillin G benzathine (OR 0.68: 0.29-1.6195% IC) (72). Another meta-analysis (AMSTAR score 10/11) included three RCTs which compared penicillin benzathine to azithromycin. There were no significant differences in terms of clinical cure (OR 1.04:0.69-1.5695% IC) not three months after the beginning of treatment, nor were there any differences regarding adverse events between azithromycin and penicillin benzathine (OR 1.43:0.42-4.9595% CI). The aforementioned studies involved a risk of reporting bias and limited precision; heterogeneity was high for evaluating adverse events (73) (level of evidence: moderate).

However, given that azithromycin-resistant *T. Pallidum* has been found in different parts of the world, it is recommended that this antibiotic is used only in cases where penicillin or doxycycline is not available (4, 9).

An RCT which studied ceftriaxone treatment in patients suffering primary syphilis did not reveal any differences regarding clinical or serological cure rates compared to patients treated with penicillin G benzathine (RR 0.8:0.32-1.99 95% IC). This RCT had insufficient sample size and important losses regarding follow-up and indirectness due only

male patients were included (74). The optimum treatment dose and timing of Ceftriaxone treatment was not defined (4) (level of evidence: low).

Managing patients with a penicillin allergy: A retrospective cohort study of patients treated with doxycycline/ tetracycline was found. This study revealed no differences regarding serological cure rate in patients diagnosed with syphilis who had been treated with doxycycline/ tetracycline after 12-24 months, compared to patients treated with penicillin G benzathine (RR 1.0: 0.95-1.0695% IC). There was no difference in the time taken to serological cure between the two treatments. (Median 43 and 72, respectively; $p=0.16$). This study had a high risk of bias regarding selection, confounding and evaluating adherence to treatment. It was not clear whether patients having documented penicillin allergy were included or which criteria were used for prescribing doxycycline (75) (level of evidence: very low).

Treating chancroid: An RCT, which included 184 men suspected of suffering chancroid infection (127 had a positive culture for *H ducreyi*) with 83% follow-up, compared treatment with azithromycin to erythromycin. There was no difference in clinical cure rates between the two treatments. (OR 0.97: 0.86-1.1095% CI) (76). This study had a high risk of bias related to unclear random assignment and concealment methods and because it was un-blinded. Another RCT with risk of bias (performance and detection bias unclear and lack of adherence to the assignment of treatment), which included 133 patients suffering *Haemophilus ducreyi* infection, also did not show differences between azithromycin or ceftriaxone use of in terms of clinical cure (RR 1.13: 0.98-1.3095% CI) or adverse events (RR 2.02: 0.92-4.4395% CI) (77) (level of evidence: moderate).

An RCT involving 208 men and 37 women with confirmed *H. ducreyi* infection compared treatment with Ciprofloxacin (500mg single oral dose) to

erythromycin (500mg 3 times a day for 7 days). The ciprofloxacin group had 19% treatment failure compared to 12% for the erythromycin group. No significant differences were found in terms of the clinical cure rates 21 days after beginning the treatment (RR 0.97: 0.68-1.3695% CI) (78) (high level of evidence).

CDC guidelines (4) have indicated that reports of *Haemophilus ducreyi* resistance to ciprofloxacin and erythromycin are increasing, thereby suggesting that bacterial resistance studies should be undertaken in case where these drugs are used (level of evidence: low)

Treating venereal lymphogranuloma (*Chlamydia trachomatis* serotypes L1, L2, L3): An RCT which compared different tetracyclines having a similar profile to that of doxycycline (chlortetracycline, oxytetracycline and sulfadiazine) to symptomatic treatment (aspirating the buboes plus aspirin), showed shorter lesion duration (31 cf 69 days) and greater serological cure rate in the patients who were treated with an antibiotic (RR 2.33: 1.4-4.1 95% CI). However, the risk of bias in this RCT was not clear since many evaluation elements were not present as this study was published in 1957 (79) (level of evidence: low).

Azithromycin for treating venereal lymphogranuloma has not been evaluated directly and the available evidence comes from other infections caused by *C. trachomatis*. In addition to the previously described evidence, two RCTs that compared Azithromycin with doxycycline which included 971 patients with *Chlamydia trachomatis* infection (mainly urethritis and cervicitis) did find differences in terms of clinical cure (RR range 1.03-1.06), However, there was no significant difference in terms of clinical cure or bacteriological cure (RR range 0.97-1.01) or regarding the presence of adverse events (RR range 0.89-1.1) compared to patients treated with doxycycline (80, 81). It is worth noting that these trials included patients with *Chlamydia trachomatis* infection in general, i.e. not specifically due to strains related to venereal

lymphogranuloma: serovars L1, L2 and L3 (level of evidence: moderate).

Regarding erythromycin use, a report was found where 2 out of 3 patients treated with 1,600 mg daily improved after 12 and 14 months of treatment (82) (level of evidence: very low).

Treating inguinal granuloma: Little evidence is available regarding azithromycin and ciprofloxacin use. Two reports of cases involving ciprofloxacin treatment (83, 84) and an RCT pilot study concerning azithromycin use (85) were identified; no evidence was found regarding trimethoprim-sulfamethoxazole use. Experts recommended the use of doxycycline as first line regime for this infection, followed by alternative regimes such as azithromycin, ciprofloxacin, erythromycin and trimethoprim-sulfamethoxazole (4) (level of evidence: very low).

Treating first HSV infection: The effectiveness of acyclovir for treatment of first HSV infection has been evaluated in 3 RCTs, involving 259 patients suffering their first episode of herpes simplex. The trials showed a reduction in the virulence period of the infection when treated with acyclovir when compared to placebo (86-88). The RCT data involving the greatest number of patients (150 patients: 119 of them having primary infection and 31 secondary infection) showed that acyclovir significantly reduced the time for lesions to become completely cured (12 *cf* 14 days; $p=0.005$), reduced new lesion formation 48 hours after beginning the therapy (18% *cf* 62%; $p=0.001$) and reduced the duration of pain (5 *cf* 7 days; $p=0.05$) and viral shedding (2 *cf* 9 days; $p<0.001$) (87). However, two of the studies had low sample sizes (level of evidence: moderate).

A multicentre RCT compared valaciclovir ($n=323$) to acyclovir ($n=320$) as treatment for first HSV infection. It did not reveal any differences regarding the time taken until symptom resolution (HR 1.0: 0.85-1.1895% CI), virulence duration (HR

1.02: 0.85-1.2295% CI), duration of pain (HR 1.02: 0.84-1.1895% CI) or adverse events. This study had a low risk of bias (89) (level of evidence: high).

Treating recurrent herpes: Recurrent herpes has been defined as 6 or more episodes during a single year (9). A systematic review involving a meta-analysis of 14 RCTs (AMSTAR 9/11) showed that recurrent episodes of genital herpes were reduced with acyclovir (RR 0.46:0.43-0.4995% CI), valacyclovir (RR 0.56:0.53-0.5995% CI) or famciclovir treatment (RR 0.57: 0.5-0.6595% CI) (90) (level of evidence: high).

Experts have suggested that treatment with acyclovir or valacyclovir as prophylaxis for recurrent genital herpes must continue for 1 year(4) (level of evidence: very low).

23. Which complications are associated with GUS?

Complications related to treating genital ulcers do not occur very frequently, but when they arise, they may represent a failure to diagnose the initial infection and therefore modifications to the treatment may be required. Therapeutic failure is the main complication which may present when adopting a syndromic approach to treating genital ulcers; this can be assessed during follow-up or during patient consultation following initial prescription. An example of this would be the appearance of systemic infection (secondary or tertiary syphilis) (91). Factors such as initial syndromic diagnosis, co-infection with other STI/GTI, the presence of HIV infection, adherence to treatment or the aetiological agent's resistance to the recommended treatment must be considered when determining the next course of treatment. (4).

In some cases, the infection itself brings about complications, some of them related to the treatment used. The Jarisch-Herxheimer reaction is one of the most frequently occurring ones, involving an acute febrile illness, accompanied by severe headache and myalgia 24 hours after beginning

treatment for syphilis; 50% incidence has been reported in patients suffering primary syphilis treated with penicillin G, with resolution occurring within 12-24 hours of its appearance (92).

Recurrences may also be considered a complication. Recurrences occur relatively frequently in HSV infections and can be successfully treated as previously described with antivirals (93). Some symptoms, such as the presence of buboes in chancroid infection or venereal lymphogranuloma, might require another type of management in addition to pharmacological management in order to prevent the complications arising from lymphadenopathy (94, 95).

24. How are GUS patients followed-up?

<i>Strong recommendation in favour</i>	GUS patients must attend to follow up 2 weeks after beginning treatment.
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Optimum follow-up of patients suffering infections causing genital ulcers is based on expert opinion rather than clinical studies. Optimal follow-up represents a challenge for doctors dealing with these patients as often there are barriers to accessing care. The group of experts considered that clinical examination of patients was desirable at least 2 weeks after administering the recommended treatment when syndromic management of genital ulcers had been adopted. This is to ensure treatment had been effective and if not, to establish whether a different aetiological cause of the infection could be the cause (level of evidence: very low).

25. How are the partners of patients suffering from GUS treated?

<i>Weak recommendation in favour</i>	The partners of patients diagnosed as suffering GUS must be treated. EPT for GUS patients' sexual contacts made during the last 90 days is recommended, using the treatment
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	regime recommended for index patients. A single intramuscular dose of 2,400,000 IU penicillin G benzathine is recommended for treating syphilis plus single oral dose 1 g azithromycin (covering <i>H. ducreyi</i>). Only in cases of documented penicillin allergy should an oral dose of 100 mg doxycycline be given twice a day for 14 days. An oral dose of 200 mg acyclovir should be administered 5 times a day for 6 days to the partners of any patient suspected of suffering HSV infection.
<i>Weak recommendation in favour</i>	A consultation is recommended during which the sexual contacts receive counselling and treatment for STIs.
<i>Weak recommendation in favour</i>	Sexual health consultations should be held in a suitable setting where the same level of privacy and confidentiality to that of HIV counselling can take place. Diagnosis and treatment should be started on first contact with the index/primary patient.

Treating a sexual partner: Two recent CPGs have agreed on the importance of clinically reviewing the sexual partners of patients suffering from any of the infections which cause GUS (4, 9). Consultations are aimed at reviewing signs and symptoms and determining appropriate treatment. The CPGs concluded that treatment should be given in all cases, even in the absence of symptoms for sexual partners of those suffering from venereal lymphogranuloma, chancroid, inguinal granuloma and syphilis. The CPGs concluded that sexual partners of those suffering from herpes infection should be offered a consultation, but treatment was a priority only for patients with symptoms (level of evidence: very low).

A Systematic Review examining methods for notifying partners included an RCT of patients suffering syphilis infection. The RCT found that the contract notification method managed to locate more partners than the provider notification method (difference of means = 2.2:1.95-2.4595% CI); however, the group of partners receiving treatment was the same in both groups (46) (level of evidence: moderate).

26. How is GUS treated in pregnant or breastfeeding women?

<i>Strong recommendation in favour</i>	<p>A single intramuscular dose of 2,400,000 IU penicillin G benzathine (for treating syphilis) plus single oral dose 1g azithromycin (covering <i>H. ducreyi</i>) should be used for the syndromic management of genital ulcers in pregnant or breast feeding women. In women with documented evidence of penicillin allergy, the same medication should be supplied, following desensitisation. In addition to the above, one of the following should be added:</p> <ul style="list-style-type: none"> • When HSV infection is suspected, oral 200 mg acyclovir 5 times a day for 6 days should be added; • When venereal lymphogranuloma is suspected, oral 1 g azithromycin should be added per week for 3 weeks or until the lesions disappear; and/or • When inguinal granuloma is suspected, oral 500 mg erythromycin should be added 4 times a day for at least 3 weeks or until the lesions disappear (erythromycin estolate must not be given to pregnant females)
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<i>Strong recommendation in favour</i>	A single intramuscular dose of 2,400,000 IU penicillin G benzathine (following desensitisation) should be used for treating pregnant or breastfeeding women with a confirmed diagnosis of primary syphilis and history of penicillin allergy.
<i>Strong recommendation in favour</i>	A single intramuscular dose of 250 mg ceftriaxone should be used as second line treatment for pregnant or breastfeeding women suspected of having <i>Haemophilus ducreyi</i> infection, when azithromycin is not available or there are contraindications to its use. When ceftriaxone is not available, an oral 500 mg dose of erythromycin should be given 4 times a day for 21 days as a third line option (erythromycin estolate must not be given to pregnant women).
<i>Strong recommendation in favour</i>	An oral 1 g dose of azithromycin once a week for 3 weeks should be used as first line treatment for pregnant or breastfeeding women suspected of having venereal lymphogranuloma infection and should be used until the lesions disappear.
<i>Weak recommendation in favour</i>	An oral dose of 500 mg erythromycin 4 times a day for 21 days (erythromycin estolate must not be administered to pregnant women) should be used for treating pregnant or breastfeeding women suspected of suffering venereal lymphogranuloma infection when azithromycin is not available or there are contraindications to its use.
<i>Weak recommendation in favour</i>	An oral 500 mg dose of erythromycin should be used 4 times a day for at least 3 weeks or until the lesions have disappeared as the first line option for treating pregnant or breast-

	feeding women suspected of having genital infection caused by inguinal granuloma (erythromycin stolate must not be administered to pregnant women).
<i>Strong recommendation in favour</i>	An oral dose of 400 mg acyclovir should be used 5 times a day for 6 days as the first line treatment for pregnant or breastfeeding women suffering their first or recurrent episodes of genital infection caused by herpes simplex type 1 or 2.
<i>Strong recommendation in favour</i>	Syndromic management is suggested for pregnant or breastfeeding women suffering genital ulcers, together with opportune referral to prenatal clinic for tests to confirm the infection's aetiology.

Treating early syphilis in pregnant women:

A systematic review of observational studies (AMSTAR 6/11) which included studies on pregnant women referred to screening and the early treatment of active syphilis with 2,400,000 IU penicillin benzathine in different countries, having moderate heterogeneity, showed a reduction in the risk of congenital syphilis (RR = 0.03: 0.02-0.07 95% CI), foetal demise (RR = 0.18: 0.10-0.33 95% CI), preterm birth (RR = 0.36: 0.27-0.47 95% CI) and neonatal death (RR = 0.20: 0.13-0.32 95% CI) (96)(level of evidence: low).

A systematic review (AMSTAR 9/11) was evaluated which assessed antibiotic (AB) effectiveness with regards to treating syphilis during pregnancy (97). Even though 29 studies were localised, they did not fulfil quality and design criteria to be considered as candidates for the review.

Treatment of Chancroid. No evidence was found regarding how chancroid should be treated in pregnant women; only indirect information was available regarding effectiveness in other

populations having limited external validity. No evidence concerning treatment of venereal lymphogranuloma or inguinal granuloma in pregnant or breastfeeding women was found; only the aforementioned evidence about treating the conditions in non-pregnant women. The Canadian guidelines (9) recommended the use of erythromycin for treating pregnant women suffering *Lymphogranuloma venereum* (LGV); however, our experts prioritised azithromycin to promote adherence (level of evidence: very low).

27. How are pregnant or breastfeeding women suffering their first episode of genital infection (suspected) caused by HSV type 1 or 2 treated?

No evidence was found regarding the treatment of HSV in pregnant women; only the aforementioned information was available regarding effectiveness in non-pregnant women, having limited external validity (level of evidence: very low).

28. Which complications most frequently present in pregnant women suffering from GUS?

In addition to the aforementioned complications, the most frequently occurring complications for pregnant women suffering genital ulcers are those related to giving birth and the newborn (98) the complications associated with the various medications commonly administered for treating different infectious agents have not been fully established. It is well-known that some reactions (such as the Jarisch-Herxheimer reaction) in maternal syphilis affect up to 40% of pregnant women and is associated with the appearance of uterine contractions, preterm birth and deceleration of the foetal cardiac rate, with no serious outcomes at the end Using acetaminophen for managing pain and the associated fever has been shown to be useful (98).

When transmission of an infection to the foetus occurs during pregnancy or labour, it carries a high burden of morbidity and mortality for the newborn. Congenital syphilis is a multiple organ infection which impacts severely on neurological and skeletal development of the new born and can cause infant mortality (99). It is known that screening for the condition and early treatment of pregnant women can effectively avoid such transmission (96). Neonatal herpes is another example of a complication arising from transmission of the infection at birth, especially when the mother is affected in the last trimester of pregnancy (100).

VAGINAL DISCHARGE SYNDROME

29. Which aetiological agents are associated with vaginal discharge syndrome (VDS)?

Most patients suffering vaginal discharge do not have a sexually-transmitted infection (5,101). There are three main causes of vaginal discharge syndrome (VDS): bacterial vaginosis, candidiasis and trichomoniasis. Concomitant infection by BV and *Candida albicans* has been described in 7.5% of patients (5). *C. trachomatis* and *N. gonorrhoea* may also be causal agents in patients who have risk factors for STI (5) (level of evidence: moderate).

30. Which clinical manifestations of STI/GTI are characterised by VDS?

Various signs and symptoms have been described for diagnosing pathologies associated with VDS; these include foetid vaginal discharge (most frequently associated with bacterial vaginosis), yellow discharge in trichomoniasis and vaginal and/or vulvar pruritus and erythema and dysuria, most frequently associated with candidiasis (8, 49). Initial syndromic management does not include laboratory tests.

31. Which is the most effective and safest treatment for VDS?

<i>Strong recommendation in favour</i>	An oral dose of 2.0 g tynidazole should be used for the syndromic management of patients suffering vaginal discharge. If concomitant <i>Candida albicans</i> infection is suspected, then a single oral dose of 150 mg fluconazole should be added*. When tynidazole is not available, then a single oral dose of 2 g secnidazole should be used as secondline treatment option. In cases of contraindications to imidazole treatment or if secnidazole is not available, then 5 g intravaginal 2% clindamycin vaginal cream should be used once a day for seven days as the third line treatment option. When fluconazole is not available or there are contraindications, then a single vaginal dose of 500 mg clotrimazole should be used as second line option.
<i>Equity recommendation Strong recommendation in favour</i>	A single oral dose (2 g tynidazole + 150 mg fluconazole*) is suggested for treating vaginal discharge in women in disadvantaged populations (poverty situation and sexual workers)
<i>Strong recommendation in favour</i>	The first line treatment option for patients suffering suspected VDS or where the presence of <i>Trichomonas vaginalis</i> has been confirmed, should be a single oral dose of 2 g tynidazole. When tynidazole is not available, a single oral dose of 2 g methronidazole should be used as the secondline option.
<i>Strong recommendation in favour</i>	Patients should be counselled about not drinking alcohol during treatment involving methronidazole

or tynidazole. Abstinence should be maintained up to 24 hours after finishing therapy with methronidazole and up to 72 hours with tynidazole.

*Fluconazole significantly increases the plasma concentration (i.e. haematological values) of phenylhydantoin, astemizole, calcium channel blockers, cisapride, oral hypoglycemics, rifampicin, zidovudine, rifabutin, cyclosporine, sulfonyleureas and warfarin. It slightly modifies the metabolism of the ophylline, terfenadine and oral contraceptives. Subjects receiving more than 400 mg a day or hyperazoemics may infrequently present with drug interactions.

Treating VDS: An RCT was analysed which compared single-dose syndromic management of vaginal discharge with tynidazole and fluconazole to syndromic management with methronidazole and clotrimazole lasting the conventional duration of treatment. The study recruited women attending primary care establishments from four countries in western Africa, including sex workers and HIV patients (random assignation was stratified according to whether subjects were sex workers). No statistically significant differences were found regarding the clinical improvement rates reported by patients after 14 days (66.3% *cf* 63.9%; $p=0.26$), or after 28 days (80.9% *cf* 81.1%; $p=1.00$). Analysis by subgroup according to HIV infection status did not reveal significant differences between both treatments with regards to clinical improvement reported after 14 days, in both sero negative patients and HIV infected patients. Loss of follow up: 20%. (102) (level of evidence: moderate).

The study's results suggested that there were no differences between single-dose treatment and conventional treatment when comparing them for the syndromic management of vaginal discharge (the difference between them being less than 10%). A single dose was suggested due to patient preference and the possibility of promoting better adherence to treatment, especially in disadvantaged populations; for example, it should be born in mind that sex workers activities and income are related to their ability to maintain an (extremely) active sex life. The validity of this recommendation will

remain open until the CPG is next updated. Studies including subgroup analysis are required to improve the available evidence, specifically for sex workers and other vulnerable populations.

Treating bacterial vaginosis: A meta-analysis which included 24 controlled clinical trials (4,422 participants; AMSTAR score 8/11) which compared several treatments against placebo and between themselves in terms of clinical failure found that topical metronidazole was more effectiveness when compared to placebo (RR 0.59:0.44–0.79 95% CI), and Vaginal clindamycin was more effectiveness when compared to placebo (RR 0.19: 0.09–0.4195% CI). Comparing metronidazole to clindamycin revealed a similar clinical failure rate after 7 days (RR 1.06: 0.64-1.75 95% CI) and after 28 days (RR 0.97: 0.75-1.2795% CI). The metronidazole plus azithromycin combination compared to metronidazole alone was more effective for avoiding clinical failure after 7 days (RR 0.65: 0.46-0.9295% CI) and equally effective after 28 days (RR 1.22: 0.82-1.8395% CI). No differences were found between single dose tynidazole and metronidazole after 7 days treatment with regards to clinical failure (RR range 0.38-1.73) or adverse events (RR 0.62:0.13-2.9895% CI). There were no differences between methronidazole and clindamycin treatment with regards to discontinuing treatment, (RR 0.50 0.17-1.4795% CI), adverse events (RR 0.75: 0.54-1.0595% CI) or *Candida albicans* cell envelope (RR 1.11: 0.78–1.5895% CI). There were fewer adverse events with clindamycin treatment opposed to metronidazole, which caused nausea (RR 0.27: 0.11–0.6995% CI). No evidence was found supporting the use of lactobacillus, triple sulphonamide vaginal cream, polyhexamethylene biguanide for shower use, oxygen peroxide, cephadroxyl (103).

One RCT did not find any differences between single dose secnidazole and metronidazole for 7 days with regards to clinical cure (RR 0.97: 0.88-1.0895% CI) or bacteriological cure (RR 1.03: 0.91-

1.1795% CI) after 28 days. There was no difference with regards to adverse events (RR 0.94: 0.74–1.1495% CI)(104) (level of evidence: moderate).

Treating *Trichomonas vaginalis*: A meta-analysis (AMSTAR score 9/11) was evaluated which included 54 controlled clinical trials (5,201 patients) comparing several treatments to no treatment in terms of infection persistence after 4 to 14 days. Lower infection persistence was demonstrated in the treatment arm with imidazol (RR 0.50: 0.43–0.5695% CI). Short-term and long-term treatment with imidazole was also compared in terms of failure of cure; no differences were found between the two groups (RR 1.12: 0.58–2.1695% CI) involving follow-up for up to 35 days. A lower risk of persistent infection after 21 days was demonstrated for the oral route when comparing oral to vaginal treatment aimed at cure (RR 0.20: 0.07–0.5695% CI). Comparing methronidazole to tynidazole revealed a higher percentage of clinical in favour of tynidazole, at to 21 days follow-up 3 (RR 3.81: 1.83–7.9095% CI) and parasitological cure (RR 3.24: 1.66–6.3295% CI). Secondary adverse effects were more common with metronidazole than with tynidazole treatment (RR 1.65: 1.35–2.0295% CI). This systematic review had a unclear risk of bias with regards to the included studies and there was a high level of heterogeneity with regards to some of the comparisons (105) (level of evidence: low).

Treating *Candida albicans*: A meta-analysis of the literature was found which evaluated managing *Candida albicans* (AMSTAR score 9/11); it included 19 controlled clinical trials (2,579 patients). No statistically significant differences were found between oral and vaginal therapy (fluconazole vs clotrimazole) with regards to short-term microbiological cure (RR 1.02: 0.98–1.0795% CI) to long terms (RR 1.01: 0.93–1.0995% CI) or clinical improvement rates to short term (RR 0.92: 0.81–1.0595% CI) and clinical improvement to long terms (RR 1.00: 0.92–1.0895% CI). Just two

of the 19 clinical trials included in this systematic review reported therapy being abandoned due to the presence of an adverse reaction to treatment; one case happened in each study (not specified). The review's authors stated that no conclusion could be drawn concerning the safety of treatment involving oral or vaginal therapy for uncomplicated candidiasis. The included studies had a high risk of bias because there was no concealment, higher than 20% loss to follow-up and CCTs had often been funded by pharmaceutical companies (106) (level of evidence: low).

32. How are VDS patients followed-up?

<i>Strong recommendation in favour</i>	Vaginal discharge patients should be instructed to return for a follow-up visit if the symptoms persist or reappear within the first two months following the start of treatment.
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Routine follow-up of BV patients is not necessary, unless the symptoms recur or the patient is pregnant. (4, 9).

33. How effective and/or safe is treating persistent or recurrent vaginal discharge?

<i>Weak recommendation in favour</i>	Metronidazole vaginal ovules should be used twice a week for 4 months for prophylaxis of recurrent or persistent BV.
<i>Strong recommendation in favour</i>	1 g clotrimazole cream should be used once a month for 6 months for treating recurrent or persistent vaginal candidiasis.
<i>Strong recommendation in favour</i>	When clotrimazole is not available or there are contraindications to its use, then an oral dose of 150 mg fluconazole weekly for 6 months should be provided as second line prophylactic therapy.

Good practice point

Recurrent vulvovaginal candidiasis is defined as the presence of four or more symptomatic episodes in the same year and constitutes a very rare condition. Women suffering recurrent vaginal candidiasis must be properly clinically assessed so that underlying conditions can be ruled out (diabetes mellitus type 2, HIV etc.). Vaginal swab for culture must be obtained from patients with recurrent vaginal candidiasis to confirm the clinical diagnosis and identify unusual species, particularly *Candida glabrata* and other *Candida* species which can be observed in up to 20% of women suffering recurrent vulvovaginal candidiasis in whom the treatment has often not been effective.

Recurrent bacterial vaginosis. A multi-centre controlled clinical trial compared the efficacy of metronidazole vaginal gel to placebo in patients suffering recurrent bacterial vaginosis (112 patients). The trial revealed a reduced risk of recurrence of BV on ending treatment with metronidazole gel when compared to placebo (RR = 0.43: 0.25-0.7395% CI) and 3 months post-treatment (RR = 0.68: 0.49-0.9395% CI). A high risk of bias and imprecision was found (107) (level of evidence: low).

Recurrent *Trichomonas vaginalis*. Vaginitis caused by metronidazole-resistant *Trichomonas vaginalis* is an emergent problem, the incidence of which is yet to be established (108). However, recurrent infection caused by *Trichomonas vaginalis* can usually be explained by re-infection involving an untreated sexual partner or, to a lesser degree, by a relapse. Cases of relapse are most commonly secondary to inadequate initial treatment and

is rarely secondary resistance to therapy (108). Treatment therefore consists of administering a larger dose of metronidazole or tinidazole (i.e. an oral dose of 500 mg metronidazole twice a day for 7 days or 500 mg tinidazole every 6 hours for 7 days). The use of a condom during treatment must be insisted on to guarantee suitable treatment of sexual partners. It should be stressed that tinidazole has potential advantages over metronidazole as it has more potent antimicrobial activity in vitro, a longer half-life and has fewer adverse effects (109) (level of evidence: very low).

Recurrent candidiasis. The presence of four or more episodes during a 12-month period is considered recurrent vulvovaginal candidiasis (vaginal thrush) (9). Fluconazole-resistant *Candida albicans* is usually not very frequent, having up to 13% estimated prevalence within some populations (110). However, recent epidemiological studies have indicated that non-*albicans* *Candida* species are usually found in 10% to 20% of patients suffering recurrent vulvovaginal candidiasis and it is well-known that conventional anti-fungicidal therapy is not effective against these species (9). Isolating and identifying the respective specie should thus be the rule in patients suffering recurrent or persistent vulvovaginal candidiasis, aimed at providing goal-directed therapy (9). (level of evidence: very low).

A clinical trial which included 494 women suffering microbiologically-confirmed recurrent vaginal candidiasis, compared sequential therapy which involved 150 mg fluconazole weekly for 6 months to placebo. 90.8% of the patients taking fluconazole remained recurrence free compared to 35.9% of the women managed with placebo after 6 months (risk of recurrence for placebo: RR = 2.53: 2.02-3.1795% CI). The average clinical recurrence time following the start of the trial was 10.2 months in the fluconazole group and 4.0 months in the placebo group ($p < 0.001$) (111) (high level of evidence).

Another clinical trial evaluated the effectiveness of intermittent, monthly, post-menstrual therapy involving 500 mg intravaginal clotrimazole compared to placebo in 62 patients. The trial found lower rates of vaginal candidiasis infection in the group who received treatment (30.3% prophylaxis *cf* 79.35% for the placebo: $p < 0.001$). This study had a high risk of bias and low precision (112) (level of evidence: low).

34. What is the effectiveness and safety of treating the partner of a patient suffering VDS?

<i>Strong recommendation in favour</i>	A single oral dose of 2 g tinidazole should be used for simultaneously treating the sexual partner of a patient suspected of suffering <i>Trichomonas vaginalis</i> infection. When tinidazole is not available, then simultaneous treatment with a single oral dose of 2 g methronidazole should be used as the secondline option.
<i>Strong recommendation against</i>	Treating the sexual partner of a patient suffering vaginal candidiasis is not recommended.
<i>Strong recommendation against</i>	Treating the sexual partner of a patient suffering BV is not recommended.
<i>Weak recommendation in favour</i>	Expedited partner therapy (EPT) for sexual contacts made during the last 60 days of patients suffering vaginal discharge caused by <i>Trichomonas vaginalis</i> is recommended and a consultation should be arranged so that sexual contacts can receive counselling and advice regarding STIs. Empirical treatment for sexual partners should be dispensed to the patient to give to their partner, or administered to the partner at the consultation depending on what is considered most suitable in each particular case.

<i>Strong recommendation against</i>	EPT should be accompanied by a brochure containing information about administering the medication, possible adverse effects and general information about the STI which is being treated.
<i>Good practice point</i>	It is recommended that sexual partners attend the consultation aimed at counselling regarding sexually-transmitted diseases.

No systematic reviews were found evaluating the effectiveness of treating sexual partners of women suffering *Trichomonas vaginalis* or vaginal *Candidiasis* infection.

Treating the partners of patients suffering *Trichomonas vaginalis*. A controlled clinical trial was found describing treatment for the sexual partners of 137 women suffering *Trichomonas vaginalis*; it compared the administration of tinidazole to placebo use. Tinidazole was more effective in reducing index case infection persistence or recurrence after 30 days (RR =4.66: 1.41-15.3995% CI) (113). The study had a low risk of bias and good precision. The SR about strategies for partner notification showed that expedited partner treatment increased the number of partners treated compared to provider notification in *T. Vaginalis* patients (RR= 0.51: 0.35-0.6795% CI) (46) (level of evidence: moderate).

Treating the partners of patients suffering candidiasis. A controlled clinical trial was found which compared treatment with itraconazole to no treatment in sexual partners of patients suffering candidiasis (39 patients). No statistically significant differences were found in terms of microbiological cure in the index case after 7 days (RR 1.40: 0.36–5.4695% CI) nor after 30 days (RR 2.26: 0.22–22.5595% CI) nor in terms of

clinical improvement from 7 to 30 days (RR 1.95: 0.61–6.1395% CI) (114) (level of evidence: high).

Treating the partners of patients suffering bacterial vaginosis. A systematic review which included six studies (4/11Amstar score) evaluated the effect of treatment with regards to BV recurrence. All 6 studies reported no benefit from treating the partners of patients suffering BV, however the studies had a high risk of bias and low precision, concluding that no evidence had been found to support any recommendation (115).

35. How effective and/or safe is the treatment for pregnant or breastfeeding patients suffering from VDS?

<i>Strong recommendation in favour</i>	An oral dose of 500 mg metronidazole should be used every 12 hours for 7 days in the syndromic management of pregnant or breastfeeding women suffering vaginal discharge. If concomitant <i>Candida albicans</i> infection is suspected, then a 100 mg vaginal clotrimazole tablet per day should be added for a 7-day period.
<i>Strong recommendation in favour</i>	An oral dose of 500 mg metronidazole should be used every 12 hours for 7 days as the first line option for treating pregnant or breastfeeding women suspected of suffering from bacterial vaginosis. When metronidazole is not available or there are contraindications to its use, then an oral dose of 300 mg clindamycin should be used every 12 hours for 7 days as the second line option.
<i>Strong recommendation in favour</i>	A single oral dose of 2 g metronidazole should be used as the first line option for treating pregnant or breastfeeding women suffering <i>Trichomonas vaginalis</i> .

<i>Weak recommendation in favour</i>	When treating pregnant or breastfeeding women suffering <i>Trichomonas vaginalis</i> -associated VDS and metronidazole is not available or there are contraindications to its use, then a single oral dose of 2 g tinidazole should be used as the second line option.
<i>Strong recommendation in favour</i>	When metronidazole is used, it is recommended that breastfeeding is temporarily suspended during the treatment and for up to 24 hours following the last dose. If tinidazole is used, then it is recommended that breastfeeding is suspended during the treatment for up to 3 days following the last dose.
<i>Strong recommendation in favour</i>	A 100 mg vaginal clotrimazole tablet should be used every 7 days as the first line option for treating pregnant or breastfeeding women suspected of suffering vaginal candidiasis. When clotrimazole is not available or there are contraindications, then 5 g intravaginal 10.4% terconazole cream should be used for 7 days as second option.
<i>Strong recommendation in favour</i>	Patients suffering <i>Trichomonas vaginalis</i> -associated vaginal discharge should be instructed to return for a follow-up visit if the symptoms persist.
<i>Strong recommendation in favour</i>	Patients suffering <i>Candida albicans</i> -associated vaginal discharge infection should be instructed to return for a follow-up visit if the symptoms persist or recurrence episode occurs during the 2 first months following the onset of symptoms.

Treating BV in pregnant or breastfeeding women. A systematic review of the literature was found (AMSTAR score 8/11) which included

15 controlled clinical trials and involved 5,888 participants. Antibiotic therapy (amoxicillin or clindamycin or metronidazole) was more effective for eradicating BV in pregnant women compared to placebo (OR 0.17: 0.15–0.20 95% CI). The treatment did not reduce the risk of preterm birth (i.e. less than 37 weeks) (OR 0.91: 0.78–1.06 95% CI), premature rupture of the membranes (PROM) before going into labour (OR 0.88: 0.61–1.28 95% CI) and did not reduce the risk of puerperal infection (OR 0.67: 0.39–1.17 95% CI). Treatment had no impact on the incidence of low birth-weight (OR 0.95: 0.77–1.17 95% CI) or neonatal sepsis (OR 1.4: 0.45–4.36 95% CI). The study showed that oral antibiotics were effective in reducing the incidence of therapeutic failure (OR 0.15: 0.13–0.17 95% CI), as was vaginal clindamycin (OR 0.27: 0.21–0.35 95% CI). Early treatment (before 20 weeks had elapsed) had a beneficial effect on reducing the risk of pre-term birth before 37 weeks (OR 0.72: 0.55–0.95 95% CI) and on the incidence of low birth weight (OR 0.31: 0.13–0.57 95% CI). The study did not find any differences regarding the percentage of serious adverse events which would have necessitated interrupting the treatment or non-serious adverse events. There was a high level of heterogeneity regarding some of this SR's comparisons (116). A further systematic review published after this systematic review led to similar results (117) (level of evidence: moderate).

Treating *Trichomonas vaginalis* infection in pregnant women. A systematic review of the literature was evaluated which involved 842 patients (AMSTAR score 10/11) from two controlled clinical trials, one of them undertaken in a developing country involving symptomatic and a symptomatic women. Treatment was compared to no treatment and the results revealed lower infection persistence in the group being treated (RR = 0.11: 0.08–0.17 95% CI). The studies had a high risk of bias (118) (level of evidence: moderate).

The safety of metronidazole treatment during pregnancy. Another systematic review of the literature was found (AMSTAR score 6/11) which included 5 observational studies (four cohort studies and a case and controls study) involving 199,451 pregnant women; It compared the risk of congenital malformations in pregnant women exposed to metronidazole during the first trimester. It demonstrated that treatment with metronidazole did not increase the frequency of any congenital malformation diagnosed at birth (OR 1.08: 0.90–1.29 95% CI) (119) (level of evidence: very low). No studies were found which evaluated the safety of using tinidazole during pregnancy.

Treatment of pregnant women suffering *Candida* infection. A systematic review of the literature was evaluated (AMSTAR score 9/11) which included 10 controlled clinical trials (830 patients). It showed that clotrimazole, terconazole and miconazole were more effective than nystatin in preventing persistent vaginal infection (RR 0.32: 0.25–0.41 95% CI). Likewise, clotrimazole was more effective than the placebo in eradicating *Candida* infection (RR 0.2: 0.09–0.45 95% CI). Two controlled clinical trials included in this review (81 pregnant females) demonstrated that four-day therapy was associated with greater infection persistence compared to seven-day treatment (RR 20.48: 2.89–145.19 95% CI); however, seven-day treatment was no more effective than fourteen-day therapy (RR 0.54: 0.29–1.01 95% CI). Terconazole was as effective as clotrimazole (RR 1.33: 0.34–5.16 95% CI) This SR includes RCT with high risk of bias and imprecision (120) (level of evidence: low).

36. Which complications most frequently present in pregnant or breastfeeding women suffering from VDS?

Bacterial vaginosis. (BV) associated complications in pregnant patients described to date

have been preterm birth, chorioamnionitis, endometritis and premature rupture of the membranes (4,9). However, there is contradictory evidence concerning the true benefit of treating pregnant women suffering from BV with regards to the complications described above. According to the literature, the sole benefit of treatment is relief from the signs and symptoms related to BV infection (4). However, the benefit of treating pregnant women suffering from BV who have a history of preterm birth has been shown. In these cases, treatment decreases the risk of preterm birth, the incidence of low birth weight and premature rupture of the membranes (9). Metronidazole and clindamycin are not contraindicated in pregnancy (9), however it is known that administering vaginal clindamycin after week 20 of pregnancy is associated with negative outcomes for neonates, such as low birth weight and neonatal infections (4,9).

Trichomonas vaginalis. Infection caused by *Trichomonas vaginalis* has been associated with adverse perinatal outcomes, particularly with the presence of premature rupture of membranes, such as preterm birth (OR 1.3: 1.1-1.4 95% CI), low birthweight (OR 1.3: 1.1-1.5 95% CI) (121) and neonatal infection (122). Despite this treating TV during pregnancy has not been shown to reduce perinatal morbidity (4). Some trials have suggested an increased risk of premature and low birth weight following treatment with metronidazole, however serious methodological limitations in these studies have not allowed solid conclusions to be drawn (4). TV is a sexually-transmitted disease which has unpleasant symptoms and is associated with adverse outcomes including facilitating transmission of HIV. Therefore it is prudent to offer treatment to women suffering TV infection in pregnancy. Clinicians should counsel their patients regarding the risks and benefits of treatment (118).

Candida albicans. *Candida* usually inhabits warm areas of the body, such as the mouth, vagina, perineum and groin. The infection is usually not troublesome and women are often asymptomatic. No evidence has been found suggesting that the infection should be treated in asymptomatic women. The safety and effectiveness of single dose treatments during pregnancy has not been proven (120). A clinical study evaluated the impact of *Candida* infection in pregnancy on neonatal health, however the significance of transmission of this infection is not completely understood at present. Vulvovaginal candidiasis during pregnancy has not been shown to be harmful for the foetus (123).

SCROTAL INFLAMMATION SYNDROME

37. Which aetiological agents are associated with scrotal inflammation syndrome?

Epididymitis is usually associated with *C. trachomatis* or *N. Gonorrhoeae* infection, however it can also arise secondary to infection from enteric organisms in men who engage in active penetrative anal sex without protection (9).

38. What are the clinical features of scrotal inflammation syndrome?

Scrotal inflammation syndrome includes the presence of epididymitis, which is characterised by swelling and/or unilateral testicular pain, with or without urethral discharge and an increase in local skin temperature. There may also be erythema and oedema of the scrotal skin (11). Scrotal inflammation syndrome is not always preceded by dysuria or urethral discharge. A slight increase in polymorphonuclear (PMN) cells in urethral secretion has only been demonstrated in some cases (124).

39. What is the most effective and safest treatment for scrotal inflammation syndrome?

Weak recommendation in favour	A 100 mg dose of doxycycline should be given every 12 hours for 10 days plus a single intramuscular dose of 500 mg ceftriaxone is recommended for managing scrotal inflammation syndrome. 500 mg levofloxacin should be added every 24 hours for 10 days for men over 40 years old who practice penetrative anal sex in an active role.
Weak recommendation in favour	A 100 mg dose of doxycycline should be used every 12 hours for 10 day for treating scrotal inflammation syndrome caused by <i>Chlamydia trachomatis</i> .
Weak recommendation in favour	A single intramuscular dose of 500 mg ceftriaxone should be used as first line treatment for scrotal inflammation syndrome caused by <i>Neisseria gonorrhoeae</i> . When ceftriaxone is not available, then a single oral dose of 400 mg cefixime should be used as the second line option.
Weak recommendation in favour	A 500 mg dose of levofloxacin should be used every 24 hours for 10 days for treating scrotal inflammation syndrome caused by enteric organisms.

The use of ceftriaxone has been found to be effective for treating scrotal inflammation syndrome caused by *Neisseria gonorrhoea* from indirect evidence provided by studies analysing ceftriaxone treatment versus other antibiotics in similar syndromes caused by *Neisseria gonorrhoeae*. An RCT (59) evaluated the microbiological cure

of patients with signs and symptoms of urethritis caused by *Neisseria gonorrhoeae* following treatment with either 500 mg DU ciprofloxacin, 500 mg ceftriaxone IV SD or 2 g spectinomycin IM SD. Clinical efficacy was reported to be 90% in the ceftriaxone group, 80% in the ciprofloxacin group and 94% in the spectinomycin group (there was no further statistic analysis) (Level of evidence: low).

The available evidence for making recommendations was insufficient, therefore the Canadian Healthcare Agency's Sexually-Transmitted Infections Guidelines and the CDC guideline recommendations were adopted (Atlanta) (4,9). This decision was the consensus of experts on the topic (level of evidence: low).

Slow resolution of the symptoms and signs of scrotal inflammation, in spite of suitable treatment, should lead to a clinician to consider other diagnoses including g testicular torsion, which is a surgical emergency (125).

40. Which complications are most frequently associated with scrotal inflammation syndrome?

Scrotal inflammation syndrome has increasingly been associated with chronic epididimitis as a complication. Other complications have been described, such as chronic pain and infertility but incidence of these is very low (126).

41. What is the indicated follow-up for scrotal inflammation syndrome patients?

Weak recommendation in favour	Follow-up is recommended 2 weeks after beginning treatment for men suffering scrotal inflammation syndrome.
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According to the consensus of experts, follow-up is recommended two weeks after beginning treatment (level of evidence: very low).

42. How effective and safe is the treatment for the partner of a patient suffering from scrotal inflammation syndrome?

<i>Strong recommendation in favour</i>	Expedited partner therapy (EPT) should be offered for sexual contacts made during the last 60 days of patients suffering scrotal inflammation syndrome. Treatment consists of a single oral dose 1 g azithromycin plus a single oral dose 400 mg cefixime. 500 mg levofloxacin once a day for 10 days should be added for males who have sex with males
<i>Strong recommendation in favour</i>	It is recommended that EPT should be accompanied by an informative brochure about STIs. Partners of a patient diagnosed with scrotal inflammation syndrome must be treated.
<i>Weak recommendation in favour</i>	Sexual health consultations should be held in a suitable setting where the same level of privacy and confidentiality to that of HIV counselling can take place. Diagnosis and treatment should be started on first contact with the index/primary patient.

The group of experts welcomed the recommendations for treating the sexual partners of patients suffering *Neisseria gonorrhoeae* and *Chlamydia trachomatis* infections, as well as the recommendation for treating the partners of patients affected by Gram-negative epididimitis (level of evidence: very low).

INGUINAL BUBO SYNDROME

43. Which aetiological agents are associated with inguinal bubo syndrome?

Inguinal bubo syndrome covers two separate pathologies: venereal lymphogranuloma and chancroid (4); the former results from infection by

C. trachomatis serovars L1, L2 or L3 and the latter from *H. Ducreyi* infection (95).

44. What are the clinical features of inguinal bubo syndrome?

Inguinal bubo syndrome characteristically presents with 1 or more papules or ulcers in the inguinal region, accompanied by unilateral and bilateral lymphadenopathy, called buboes (95).

In the case of chancroid, the ulcer begins as a papule which evolves into one or more pustular lesions. When these rupture, painful ulcerations are produced with an associated purulent discharge and a granulomatous base which may or may not be accompanied by active bleeding. The location of the lesion varies according to the patient's gender. In men, the lesions frequently occur on the prepuce, the balano prepuce groove and the base of the penis. In men and women, the lesions can occur on the external genitals (frequently found in the vaginal or cervical region) (127). Painful inguinal lymphadenopathy occurs in 30% of patients suffering chancroid. Chancroid can often be mistaken for syphilis during the soft chancre phase, however, the distinguishing feature is that a chancroid ulcer is painful, whereas a chancre is usually painless (9).

45. What is the most effective and safest treatment for inguinal bubo syndrome?

<i>Weak recommendation in favour</i>	An oral dose of 100 mg doxycycline should be given every 12 hours for 21 days plus a single oral dose of 1 g azithromycin for the syndromic management of patients suspected of suffering inguinal bubo.
<i>Weak recommendation in favour</i>	An oral dose of 100 mg doxycycline should be given every 12 hours for 21 days as the first line option for treating patients suspected of suffering inguinal bubo syndrome produced by venereal lymphogranuloma.

<i>Weak recommendation in favour</i>	When doxycycline is not available or contraindications to its use are present, then an oral dose of 500 mg erythromycin should be used every 6 hours for 21 days as the second line option. When erythromycin is not available, then an oral dose of 1 g azithromycin once a week for 3 weeks should be used as the third line option.
<i>Weak recommendation in favour</i>	A single oral dose of 1 g azithromycin should be used as the first line option for treating patients suspected of suffering inguinal bubo syndrome produced by chancroid. When azithromycin is not available or contraindications to its use are present, then a single intramuscular dose of 500 mg ceftriaxone should be given.

Insufficient evidence was found to make recommendations on the treatment of inguinal bubo syndrome, therefore the recommendations made by CDC (Atlanta) for sexually-transmitted infections (4), the Canadian Healthcare Agency (9) and expert consensus have been adopted (level of evidence: very low).

46. Which complications most frequently present in inguinal bubo syndrome?

Venereal lymphogranuloma responds well to antibiotic treatment, however if it is left untreated, an extensive lesion of the tissue can occur, leading to complicated abscesses, chronic fistula formation and chronic pelvic-abdominal pain (128). Proctitis caused by venereal lymphogranuloma is a complication of the infection which can occur in men and women. It can present with rectal ulcerations, bloody anal discharge, anal fissures and/or fistulas in the anal region which can trigger constitutional symptoms (129).

What type of follow-up is indicated for patients suffering inguinal bubo syndrome?

<i>Weak recommendation in favour</i>	Follow up for inguinal bubo syndrome patients is recommended 2 weeks after beginning treatment.
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The panel of experts recommended follow-up two weeks after commencing treatment (level of evidence: very low).

48. How effective or safe is the treatment of the partner of a patient suffering inguinal bubo syndrome?

<i>Weak recommendation in favour</i>	Expedited partner therapy (EPT) should be offered for sexual contacts made during the last 60 days of patients suffering inguinal bubo syndrome; treatment consists of an oral dose of 1 g azithromycin once a week for 3 weeks.
<i>Weak recommendation in favour</i>	EPT should be accompanied by an informative brochure about STIs. Partners of a patient who is diagnosed as suffering inguinal bubo syndrome must be offered treatment.

These recommendations are based on the available evidence on the syndromic management of genital ulcers (level of evidence: very low).

49. What is the most effective and safest treatment for pregnant or breastfeeding women suffering inguinal bubo syndrome?

<i>Weak recommendation in favour</i>	500 mg erythromycin every 6 hours for 21 days plus a single oral dose of 1 g azithromycin should be used for the syndromic management of pregnant or breastfeeding women suffering inguinal bubo syndrome.
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<p><i>Strong recommendation in favour</i></p>	<p>An oral dose of 500 mg erythromycin every 6 hours for 21 days should be used as the first line option for treating inguinal bubo syndrome produced by venereal lymphogranuloma in pregnant or breastfeeding women (erythromycin stolate must not be administered to pregnant women). When erythromycin is not available or contraindications have been found to its use, an oral dose of 1 g azithromycin should be used once a week for 3 weeks as the second line option.</p>
<p><i>Weak recommendation in favour</i></p>	<p>A single oral dose of 1 g azithromycin should be used as the first line option for treat inguinal bubo syndrome produced by chancroid in pregnant or breastfeeding women. When azithromycin is not available or contraindications to its use are found, then a single intramuscular dose of 500 mg ceftriaxone should be used as the second line option.</p>

This recommendation was based on the available evidence on the syndromic management of genital ulcers in pregnant women (level of evidence: very low).

50. What are the most frequently occurring complications of inguinal bubo syndrome in pregnant women?

Little has been described in the literature about the complications which may affect pregnant women suffering from inguinal bubo syndrome; however, if the data obtained regarding *C. trachomatis* infections is extrapolated, then the complications are related to ascending infection towards the uterus, leading to PID. If the infection is vertically transmitted, the neonate can develop an ophthalmological (trachoma) and/or pulmonary infection; in either of these cases it is recommended that Prenatal Control Guidelines should be referred to (130).

AUDIT INDICATORS

The indicators are given below, grouped by entity or the entities in charge.

Colombian Ministry of Health

- The Colombian Ministry of Health must develop a form for reporting, a database and present reports concerning the analysis of the data so collected.
- Availability of rapid tests for *C. trachomatis* and *N. Gonorrhoeae* by institution and attention level.
- Percentages of strains resistant to the antibiotics mentioned in the recommendations.

Colombian Local Secretariats of Health

- Number of subjects receiving promotion and prevention activities per institution.
- Amount of user training activities per local or regional health care organism.
- Amount of syndromic diagnoses and type of syndromic diagnosis reported to the epidemiological surveillance system per institution.
- Availability of rapid tests for *C. Trachomatis* and *N. gonorrhoeae* per institution per attention level.
- Number of patients referred to regional public health laboratories or sentinel institutions due to recurrence for aetiological and resistance study.
- Percentage of strains resistant to the antibiotics mentioned in the recommendations.

Abbreviations appearing in health care-related documents originally written in Spanish

- Healthcare-providing institution, Third party payers
- Sexual and reproductive health consultation available in institutions.
- Availability of genital tract infection consultation in the institutions.
- Opportunity for appointments regarding sexual and reproductive health.
- Opportunity for appointments regarding sexually-transmitted infections and other genital tract infections.

- Amount of user training activities per institution.
- Availability of rapid tests for *C. trachomatis* and *N. gonorrhoeae* per institution per attention level.
- Number of patients receiving medicaments for syndromic management, in the same institution the same day as the consultation.
- Amount of patients receiving medicaments for managing their partners by type of syndromic management (when required), in the same institution on the same day as the consultation.
- Amount of treatments for partners which were denied by third party payers.
- Amount of treatments for partners which were administered by third party payers.
- Amount of complaints regarding the non-availability of treatment for patients and/or partners in entities related to the syndromic management of sexually-transmitted infections
- Amount of patients remitted to regional public health laboratories or sentinel institutions for aetiological study and assessment of resistance due to recurrence.

Patients

Amount of complaints arising from the lack of availability of treating a patient and/or couple in entities related to the syndromic management of sexually-transmitted infections.

UPDATING THE GUIDELINES

The recommendations presented in these guidelines must be updated during the next three years or before hand in the case of new evidence becoming available which would modify the recommendations given here.

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PEER REVIEW

The Guideline was reviewed by people from the International Health Central American Institute Foundation (IHCAI).

DECLARATION OF EDITORIAL INDEPENDENCE

The financing entities have accompanied the preparation of the present document, there by guaranteeing the transferability and applicability of its contents to the context of the Colombian SGSSS. The scientific research work and preparation of the recommendations included in the present document were conducted independently by the Universidad Nacional de Colombia's GDG.

ALL MEMBERS OF THE GDG AND PEOPLE WHO HAVE PARTICIPATED IN THE EXPERT COLLABORATION AND EXTERNAL REVIEW HAVE DECLARED ANY CONFLICT OF INTEREST.

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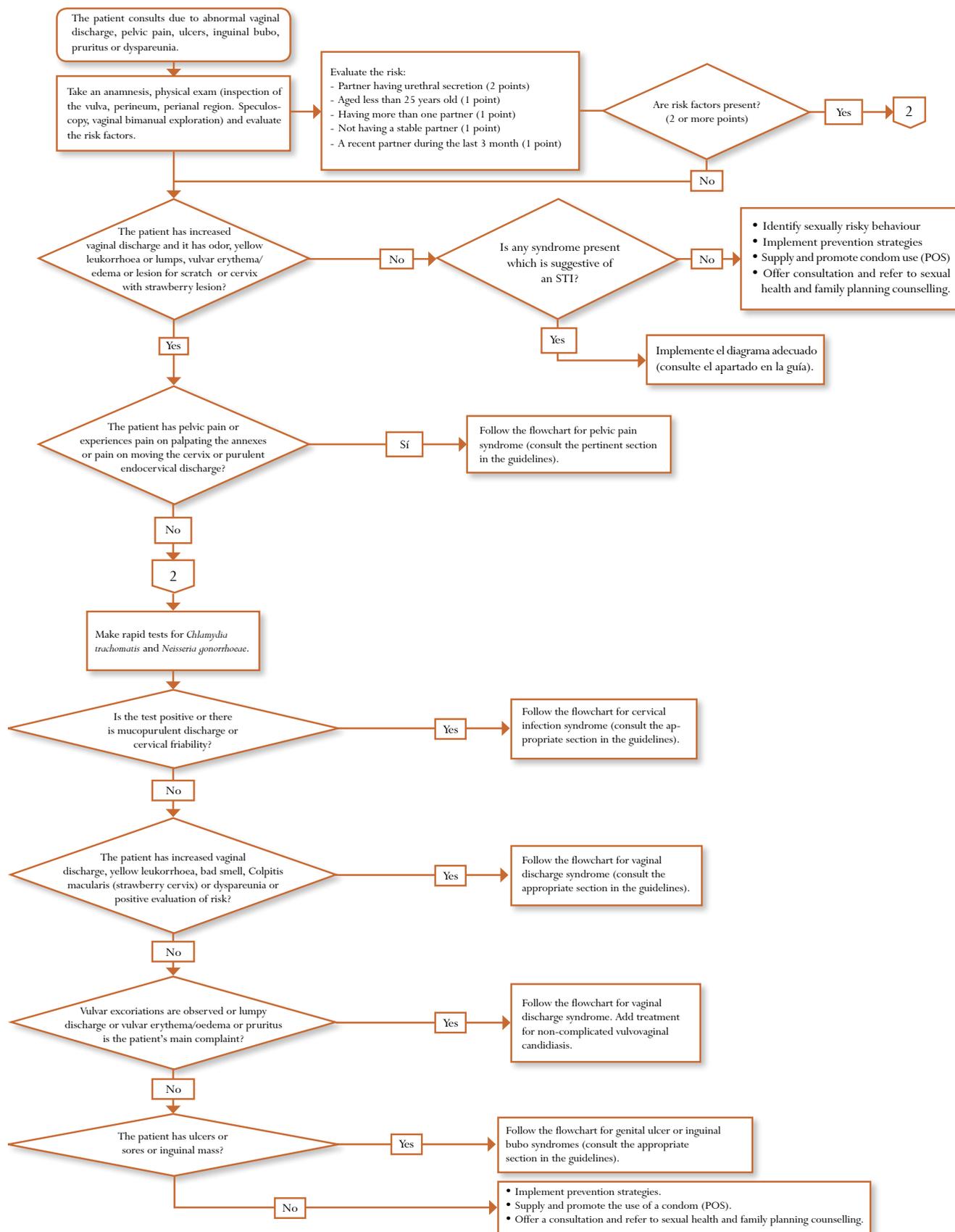
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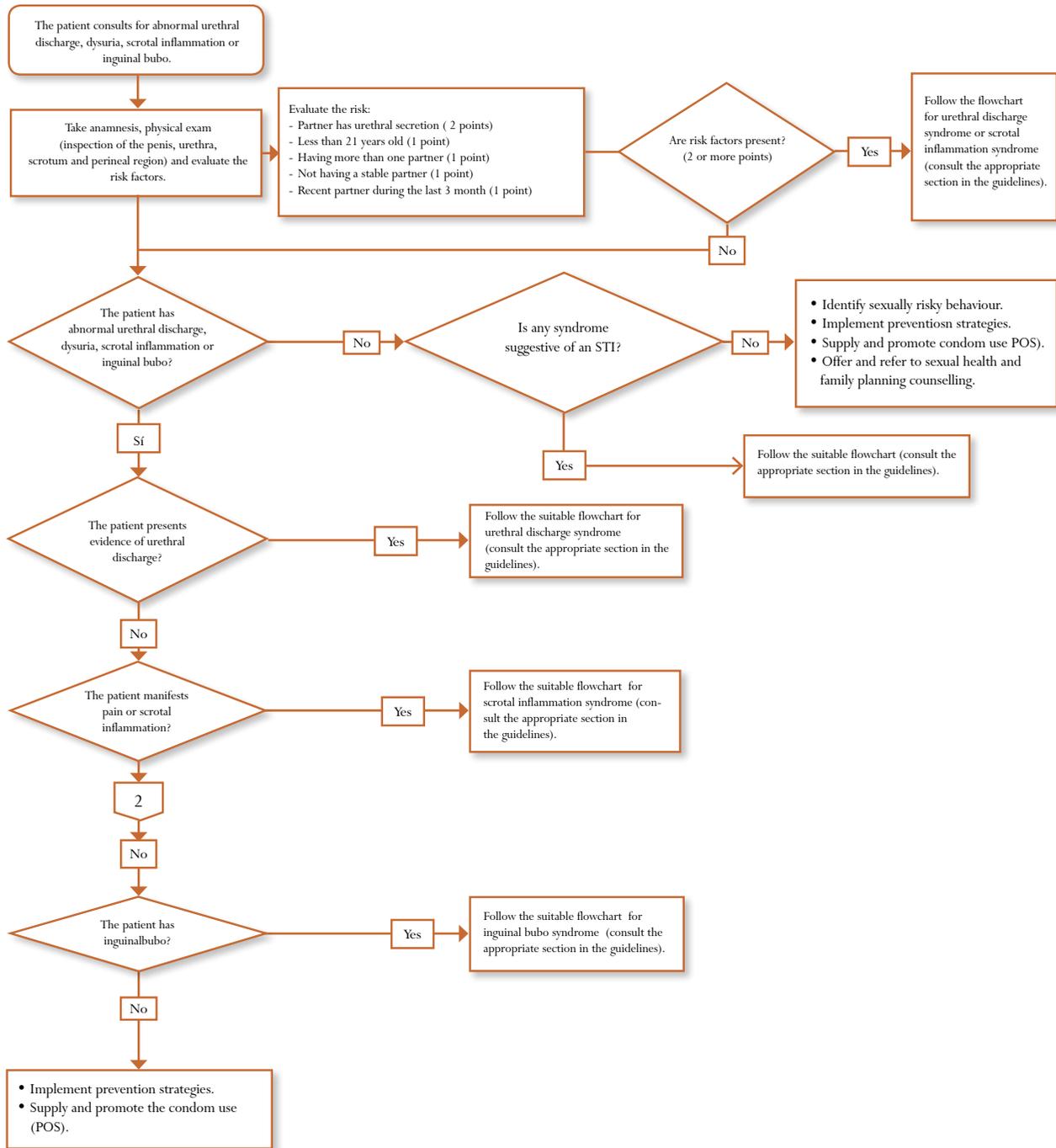
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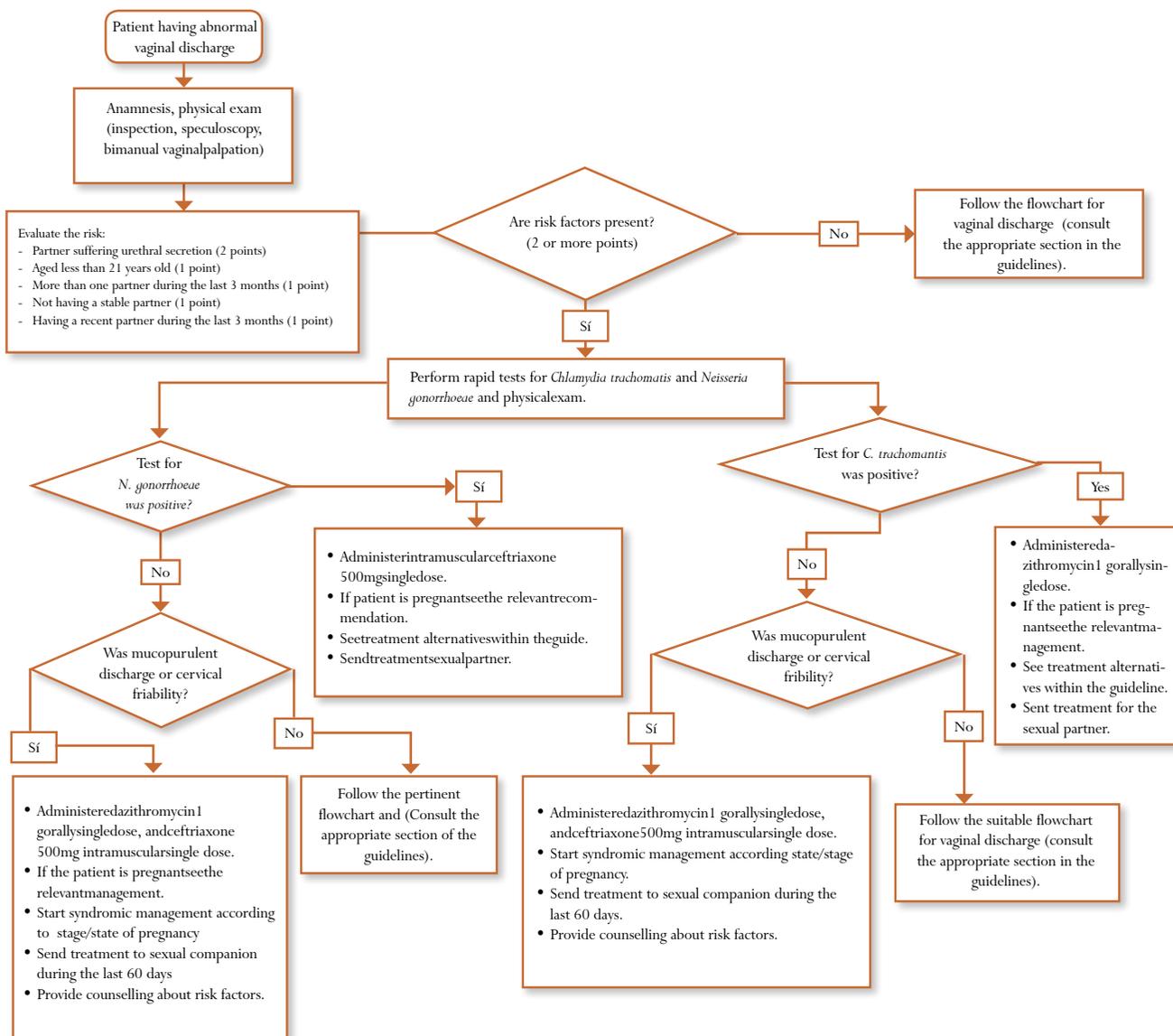
Flowchart regarding STI/GTI management in females



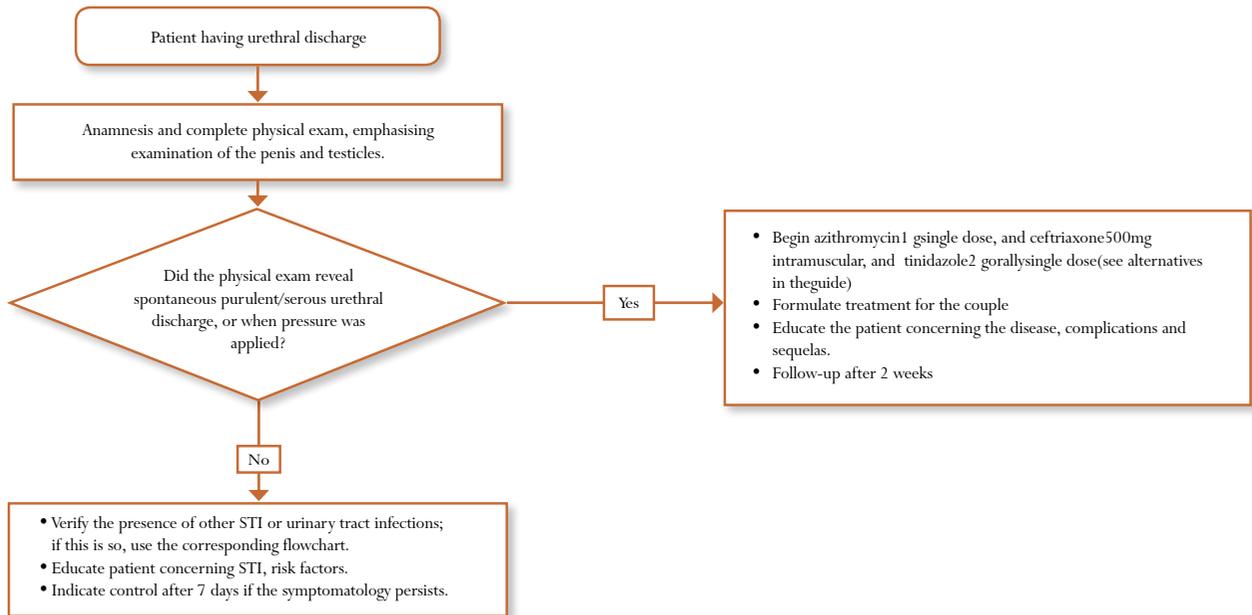
Flowchart regarding STI/GTI management in males



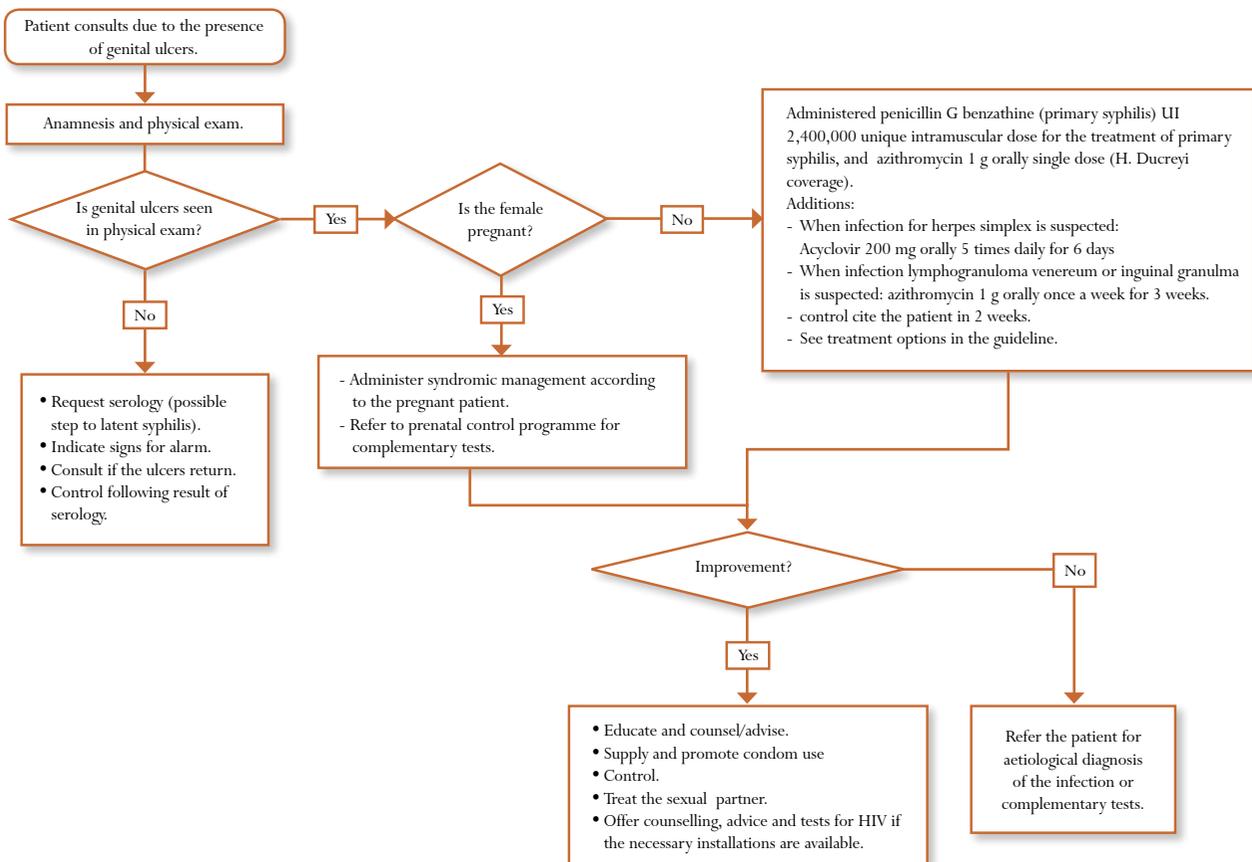
Cervicitis syndrome flowchart



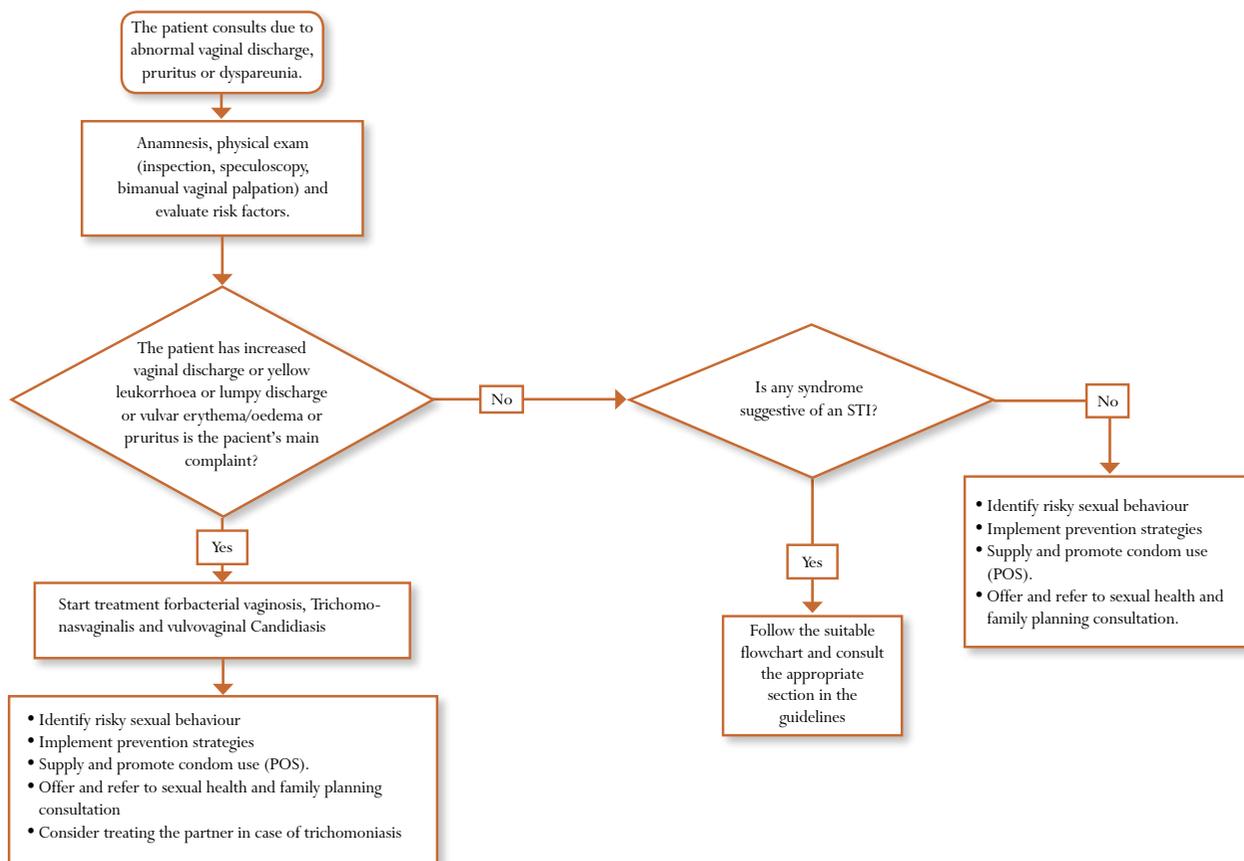
Urethral discharge syndrome flowchart



Genital ulcer syndrome flowchart



Vaginal discharge syndrome flowchart



Scrotal inflammation syndrome flowchart

