Revision of the national guideline for first-line comprehensive management and control of sexually transmitted infections: what's new and why?

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A revised national guideline for the management and control of sexually transmitted infections (STIs) has recently been published by the national Department of Health according to the Essential Drugs List. Since 2004, there has been a marked rise in resistance to ciprofloxacin among Neisseria gonorrhoeae isolates in several South African cities, requiring a change from quinolones to cephalosporins to treat presumptive gonorrhoea. In keeping with WHO recommendations, acyclovir has been added as part of first-line therapy for the management of genital ulceration. The national guideline has been revised accordingly in order to improve management of several key STI syndromes.

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Introduction

Prevention and early treatment of sexually transmitted infections (STIs) is a key public health priority in South Africa. This is reflected in the national Department of Health's HIV & AIDS and STI Strategic Plan for South Africa 2007-2011, which highlights the importance of providing quality STI services.[1]

South Africa introduced the STI syndromic management approach into primary healthcare approximately 10 years ago. Syndromic management relies on the identification of consistent groups of symptoms and easily recognised signs, and the provision of treatment that will cover the majority of, and the most serious, pathogens responsible for a given syndrome.[2] Flowcharts (algorithms) are produced which guide healthcare workers in the correct implementation of syndromic management of STIs.

The use of efficacious antimicrobial agents to treat STIs is a key component of this strategy. It is for this reason that the World Health Organization WHO recommends regular re-evaluation of syndromic management algorithms through performance of periodic aetiological and antimicrobial resistance surveys. A number of recent relevant South African-based STI surveys and research findings were made available to the Primary Healthcare Sub-Committee of the Essential Drugs Programme and to the national Department of Health in 2007, particularly in respect of changing gonococcal antimicrobial resistance patterns and the current high prevalence of herpes simplex infection as a cause of genital ulcer syndrome (GUS). As a result of these data, several key revisions were made to the existing national STI guideline.[3] This article will summarise some of these data, as well as outline the rationale for the revisions in key STI syndromic management flowcharts.

1. Evidence base for national STI guideline changes

a) Escalation of ciprofloxacin-resistant gonorrhoea

Single-dose quinolone therapy, namely ciprofloxacin, has been the mainstay of anti-gonococcal therapy in South Africa's STI treatment flowcharts for a number of years. Since 2000, the prevalence of quinolone resistance *Neisseria gonorrhoeae* (QRNG) isolates has risen dramatically in many regions of the world. Within South Africa, ciprofloxacin resistance was not reported as a clinical problem until 2003, when the sudden appearance of QRNG at a prevalence of 22% was reported from Durban, KwaZulu-Natal.[4] Subsequent surveys also revealed significant levels of quinolone resistance in Gauteng, the Western Cape and the Eastern Cape.[5-7]

In Johannesburg and Cape Town in 2007, the isolation of QRNG was significantly associated with HIV seropositivity.[7] Among the 491 men with urethral discharge who participated in the surveys, HIV seropositivity was detected at a prevalence of 39% in Johannesburg and 25% in Cape Town (author's unpublished data). HIV-seropositive men with urethritis may be

key players in the transmission of HIV to uninfected partners. In support of this concept, seminal HIV viral loads were 8-10 times higher in Malawian men with urethritis compared to control dermatological male patients.[8] It is therefore very important to ensure that the therapeutic agent used to treat presumptive gonorrhoea in syndromic management algorithms effectively treats at least 95% of patients, in line with WHO recommendations.[2]

Currently, cephalosporins are the only antimicrobials that can reliably cure gonorrhoea in most parts of the world. Among the cephalosporins, only ceftriaxone and cefixime have sufficient evidence-base to be recommended as alternatives for ciprofloxacin in the management of uncomplicated gonococcal infection.[9] Cefixime offers many advantages in that it is oral, easy to take, single dose and safe in pregnancy. At the present time, it is not manufactured in South Africa but stocks are available in the public sector through Merck (Pty) Ltd (Germany). The alternative option of ceftriaxone 250 mg as a single dose has disadvantages in that it requires intramuscular (i.m.) administration, is painful unless given with local anaesthetic (which is not allowed for safety reasons in public sector primary healthcare) and carries a risk of needle-stick injury and potential occupational HIV infection of clinical staff.

Although there are presently no global confirmed cases of clinical failure using i.m. ceftriaxone, it is worrying to note that resistance to cefixime has already been documented in Japan since 2001.[10] Ceftriaxone remains efficacious against those patients from whom cefixime-resistance gonococci are isolated. Resistance appears to be due to mosaic penicillin-binding proteins due to genetic exchange between gonococci and commensal N*eisseria* species.[11] It will be important to continue antimicrobial susceptibility surveillance programmes to monitor for cases of cefixime and/or ceftriaxone-resistant gonococci within South Africa.

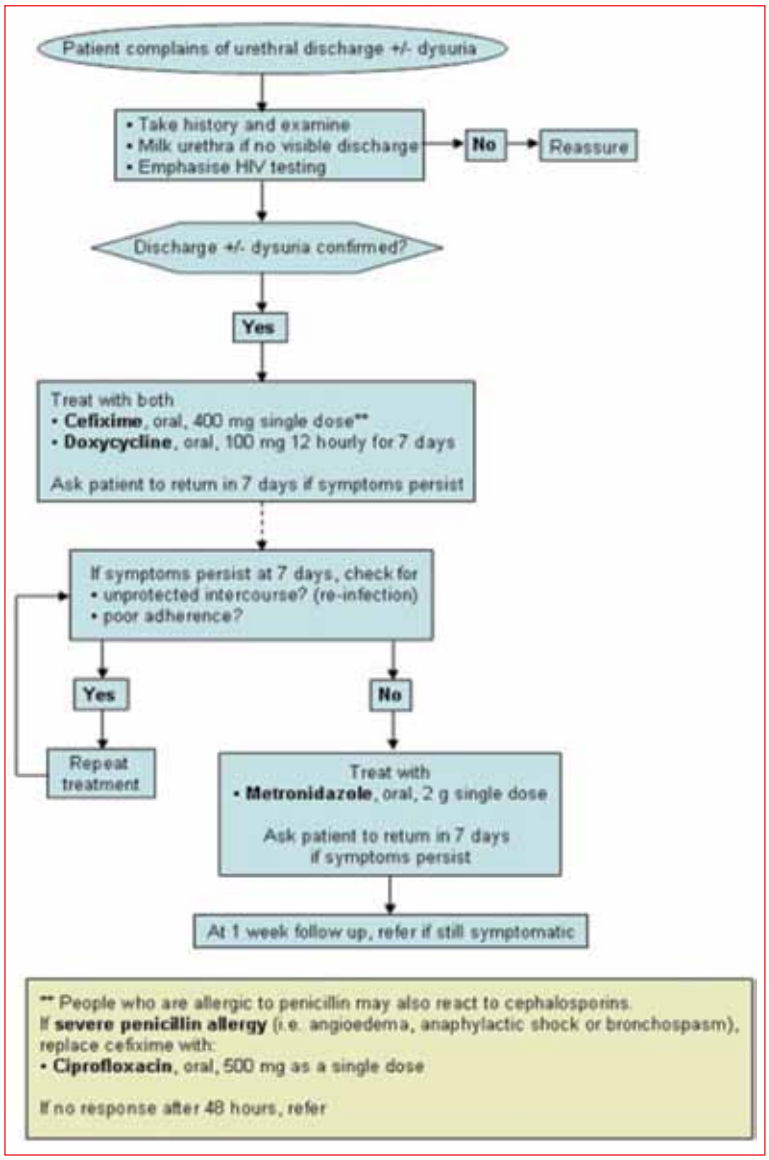

Figure 1: Male urethritis syndrome (MUS) flowchart

(adapted from the revised MUS flowchart of the Primary Health Care Standard Treatment Guidelines and Essential Drugs List, 2009)

b) Changes in genital ulcer aetiology

Until the late 1990s, bacterial rather than viral aetiologies accounted for the majority of GUS cases, particularly infection with *Haemophilus ducreyi* (chancroid) and *Treponema pallidum* (syphilis).[12] The relative prevalence of genital herpes as a GUS aetiology rose in tandem with the escalation of the HIV epidemic in the mid- to late 1990s. Since 2003, the WHO has recommended that short course acyclovir therapy be given to patients with genital ulceration when the prevalence of herpetic ulcers exceeds 30%. At the present time in South Africa, genital herpes now accounts for more than half of all genital ulcer cases, and more than 90% of genital ulcer cases in which a STI-related aetiology is detected; in most genital ulcer surveys, approximately 20-30% of cases appear negative for STI pathogens.

In 2005-2006, a randomised double-blind placebo-controlled trial (RCT) of the addition of a five-day course of acyclovir (400 mg three times daily) to conventional antibacterial syndromic therapy (benzathine penicillin for syphilis and ciprofloxacin for chancroid) for GUS was conducted among men attending primary healthcare clinics in Gauteng.[13] This study showed a significant benefit from use of acyclovir among all patients, and among HIV-infected men with a herpetic ulcer, in terms of ulcer healing, with a reduction in median healing time by self

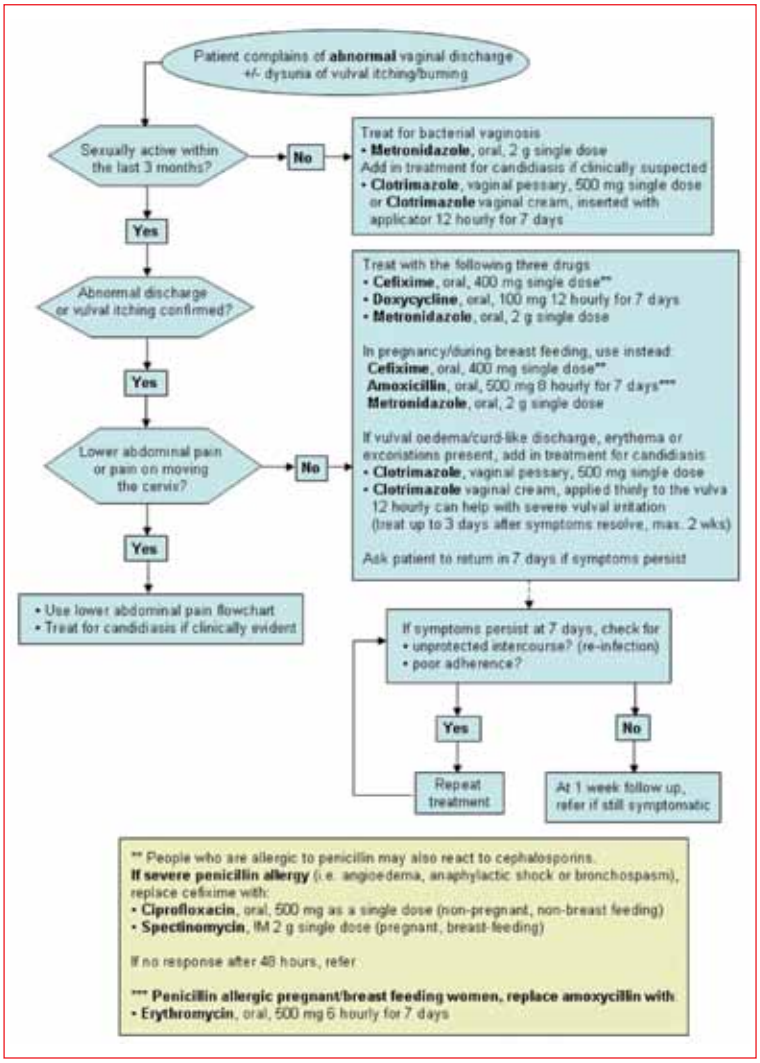

Figure 2: Vaginal discharge syndrome (VDS) flowchart

(adapted from the revised VDS flowchart of the Primary Health Care Standard Treatment Guidelines and Essential Drugs List, 2009)

report of one and three days, respectively. This study did not find any significant benefit of acyclovir therapy among those men HIV-seronegative at baseline, although the study was not powered to assess acyclovir efficacy in this subgroup. The use of acyclovir also significantly decreased the proportion of men shedding HIV from their ulcers, as well as the mean ulcer HIV RNA viral load, suggesting a possible benefit in terms of HIV transmission.

2. Summary of key changes to the STI syndromic management flowcharts

a) Emphasis on testing STI patients for HIV

In all the flow charts, the importance of discussing and offering HIV testing is emphasised (Figures 1-3). Patients with STIs are at high risk of HIV co-infection and many still remain unaware of their HIV status (especially men). Given the fact that HIV is also an STI, it remains important for clinicians and HIV counselors to remind patients to return for HIV re-testing at the end of the window period. Incident HIV infection, acquired at the same time as the presenting STI, may be missed using rapid HIV tests at the first clinic visit. It is now estimated that over 40% of new HIV infections are transmitted by individuals who have only just acquired HIV themselves, so it is important to detect HIV sero-converters through repeated HIV testing of patients with acute STIs at the end of the window period.[14]

b) Modifications to the male urethritis syndrome flowchart

The new male urethritis syndrome **(**MUS) flowchart recommends a combination of cefixime and doxycycline as therapy for presumptive gonorrhoea and *Chlamydia trachomatis* infection, respectively (Figure 1). Cefixime, as a single 400 mg oral dose, replaces ciprofloxacin 500 mg orally as the anti-gonococcal component. Cefixime was chosen for the treatment of uncomplicated MUS, as well as treatment of asymptomatic sexual partners, on the basis that this syndrome accounts for approximately 60% of male STI presentations and over one-third of men with MUS are co-infected with HIV in recent South African surveys (authors' unpublished data). Ciprofloxacin 500 mg as a single oral agent may still be given in the event of severe penicillin allergy, defined by a history of angioedema, anaphylactic shock or bronchospasm. If no clinical improvement at 48 hours, refer to hospital to access single dose spectinomycin 2 g i.m.

c) Modifications to the vaginal discharge syndrome flowchart

As with the MUS flowchart, ciprofloxacin is replaced in the vaginal discharge syndrome (VDS) flowchart by an oral single 400 mg dose cefixime (Figure 2). Cefixime may be given to both pregnant women and lactating mothers with safety. Ciprofloxacin 500 mg as a single oral agent may still be given in the event of severe penicillin allergy, defined by a history of angioedema, anaphylactic shock or bronchospasm, to non-pregnant women. If no clinical improvement at 48 hours, refer to hospital to access single dose spectinomycin 2 g i.m. In the case of pregnancy, women with severe penicillin history should be referred to hospital and treated with single dose spectinomycin 2 g i.m.

A second change in the VDS algorithm is the addition of a question box at the start of the flowchart to remind clinicians to ask women presenting with VDS as to whether or not they have been sexually active within the past three months. Those that have not are at very low risk of STIs, and should simply be treated with metromidazole 2 g as a single oral dose to cover

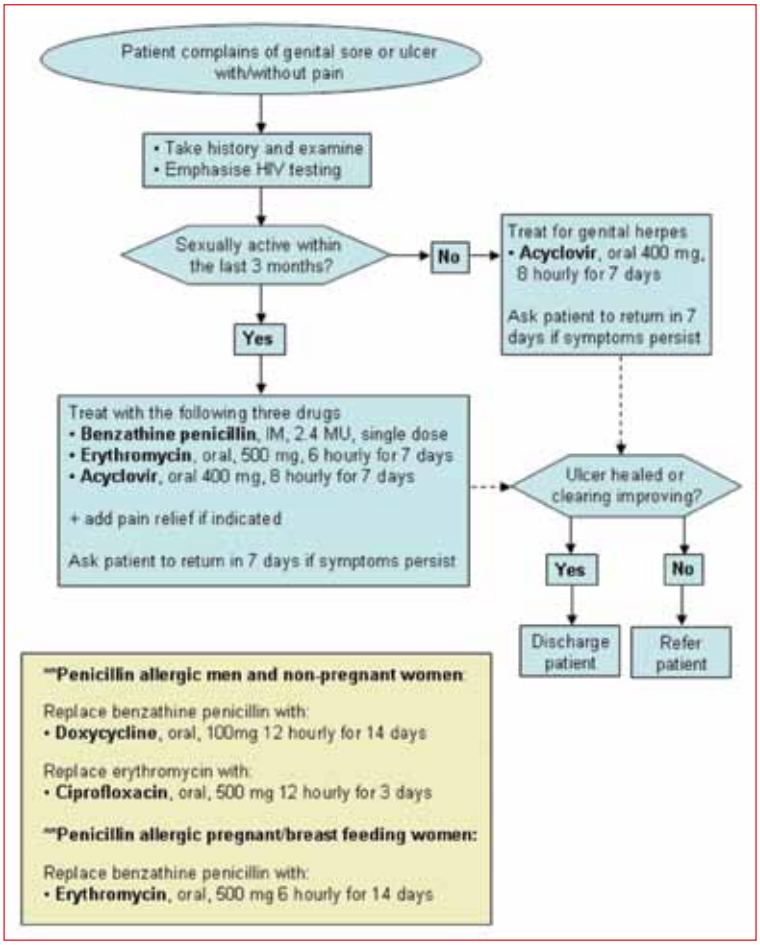

Figure 3: Genital ulcer syndrome (GUS) flowchart

(adapted from the revised GUS flowchart of the Primary Health Care Standard Treatment Guidelines and Essential Drugs List, 2009)

bacterial vaginosis. Intra-vaginal clotrimazole should be added if symptoms and/or clinical findings suggest candidiasis may be present.

A third key modification is the replacement of erythromycin by amoxycillin, given as 500 mg three times daily for one week, for the treatment of *C. trachomatis* infections in pregnancy. This change was initiated on the evidence-base outlined in a Cochrane review which showed that amoxycillin was as effective as erythromycin in achieving a microbiological cure and had the added advantage of being better tolerated.[15] The disadvantage of amoxicillin is that it is ineffective against *Mycoplasma genitalium* infection, a possible and rarer cause of cervicitis and pelvic inflammatory disease.[16-17] Should data in support of the role of *M. genitalium* as a significant reproductive tract pathogen in pregnant women emerge in the South African context, then the VDS guideline may need further revision (replacement of amoxicillin by erythromycin, or preferably, azithromycin).

Finally, the use of single oral 2 g dose metronidazole is now recommended throughout pregnancy on the basis that there is no convincing evidence that the higher single dose is harmful to the foetus. However, some clinicians may still prefer to use the longer and lower metronidazole course (400 mg twice daily for one week) in the first trimester of pregnancy in view of hypothetical concerns over higher peak serum levels of the 2 g single dose. This issue was debated at the Essential Drugs Programme Primary Care Sub-Committee during the guideline review process but it was felt there was currently no evidence-base to support the concept of withholding the 2 g dose from women in the first trimester of pregnancy.

d) *Modifications to the lower abdominal pain and scrotal swelling syndrome flowcharts*

Given the lack of evidence-base for the use of cefixime to treat presumptive gonococcal complicated infections, a decision was made to recommend a single 250 mg i.m. dose of ceftriaxone in lieu of ciprofloxacin for these two clinical syndromes.

e) *Modifications to the GUS flowchart*

The recent South African RCT showed a significant benefit in terms of ulcer healing for all participants, enhanced in the HIV-infected sub-group with proven herpetic genital ulcers. Given that most men with GUS are unaware of their HIV status (90% in the RCT), and that many men are not ready to test at the time of their clinical presentation, it was deemed most appropriate to offer acyclovir to all GUS patients. Although the RCT showed no benefit in terms of ulcer healing among HIV-negative patients, in keeping with previous literature,[18-19] it was felt it would be too complicated to have separate GUS treatment protocols for HIV-seronegative and HIV-seropositive patients.

The new GUS management guideline recognises that genital herpes now accounts for most genital ulcers (Figure 3). Based on surveys performed since 2007, syphilis is generally detected now in less than 10%, and chancroid in less than 1%, of GUS cases presenting to urban primary healthcare clinics in South Africa.[20] Therefore, the new GUS flowchart gives the option of prescribing anti-herpes therapy without the addition of antimicrobial agents for syphilis and chancroid, in patients deemed to be at low risk of having acquired an STI. A reliable history of recurrent superficial mildly painful sores in the same genital area, with or without a prior history of vesicular eruption, and particularly in the context of HIV co-infection should enable

a diagnosis of recurrent genital herpes to be made on clinical grounds, which would only require acyclovir therapy. However, the importance of taking a good sexual history cannot be over-emphasised; if the patient reports sexual exposure to a new or concurrent partner in the last three months, it would be important to cover them for the possibility of syphilis and/or chancroid regardless of the clinical appearance of the genital ulcers.

f) New algorithm for interpretation of rapid plasmin reagin testing

In order to assist with the interpretation of rapid plasmin regain (RPR) results, a new algorithm was designed and forms part of the new STI guidelines. The RPR allows measurement of both the degree of the activity of syphilis and the monitoring of the response to therapy. It is important to remember that the RPR may remain positive at a low titre after successful syphilis treatment ('serofast' result, usually ≤1:4) and so RPR titres need to reviewed in conjunction with the clinical history and presentation.

Conclusion

STI syndromic management guidelines should be regularly reviewed in the light of syndrome aetiology and antimicrobial susceptibility surveillance data. The new STI guidelines emphasise the importance of offering HIV tests to all STI patients and treatment options have been adjusted in the light of the recent rise in the prevalence of QRNG and the key role played by genital herpes in genital ulceration.

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