National Essential Drug List Medication Review Process
Primary Healthcare
Component: Sexually transmitted infections

MEDICINE REVIEW FOR THE USE OF AZITHROMYCIN IN THE SYNDROMIC MANAGEMENT ALGORITHMS FOR THE MANAGEMENT OF SEXUALLY TRANSMITTED INFECTIONS (STIs) IN SOUTH AFRICA

Date: 16 March 2014

Approach

Firstly, the use of azithromycin in modern STI management is reviewed. Following this review, a table is presented outlining the advantages/disadvantages of incorporating azithromycin to replace doxycycline in genital discharge syndromes and their complications, as well as to replace erythromycin in the treatment genital ulceration. The most important advantages and disadvantages is bolded in the table to assist the reader with prioritisation.

Properties of azithromycin that favour its use in the management of STIs

Azithromycin is an azalide derived from the macrolide class of antibiotics.[1] Compared with erythromycin, it has better oral absorption, better tissue penetration, and a wider spectrum of activity.[2] Azithromycin inhibits RNA-dependent peptide synthesis by binding to the 50S ribosomal subunit. Tissue levels are up to 100 times higher than plasma levels - tissue depletion half-life is 2-4 days.[1] After administration, azithromycin is present at high concentration in phagocytes resulting in high concentrations being delivered to the site of infection.[1] Azithromycin has activity against several bacterial STI pathogens, including *Neisseria gonorrhoeae, Chlamydia trachomatis*, *Treponemapallidum*(syphilis), *Haemophilusducreyi*(chancroid), *Mycoplasma genitalium* and *Ureaplasmaurealyticum.*Azithromycin is safe to use in pregnant women and women who are breast-feeding; this contrasts with doxycycline, which is currently the first-line treatment for presumptive chlamydial infections.

Advantages of single-dose therapies to treat STIs

For many STIs (e.g. gonorrhoea [2g], chlamydia [1g] and chancroid [1g]) azithromycin can be administered as a single dose which assists with compliance and also allows directly observed therapy to be undertaken by the attending health care provider. The World Health Organization (WHO) recommends single-dose and oral therapy as one of the key criteria for the selection of STI drugs[3]. This compares with the 7 day course of doxycycline 100mg 12-hourly that is currently used to treat presumptive chlamydial infections in many of the STI syndromes, including the male urethritis syndrome (MUS), lower abdominal pain syndrome (LAP), and vaginal discharge syndrome (VDS).

Emergence of multi-drug and extensively-drug resistant gonorrhoea

*Neisseria gonorrhoeae*has demonstrated a remarkable genetic capacity to acquire antimicrobial resistance determinants. With the development of widespread resistance to the fluoroquinolones, South Africa, along with most countries in the world, moved to the use of third generation extended spectrum cephalosporins (ESCs) as first-line therapy for gonorrhoea. Many regard ESCs as the last antimicrobial agent class suitable for widespread single-dose single-agent therapy. Among the oral ESCs, only cefixime has met the criterion on the lower bound of the 95% confidence interval for effective treatment of pharyngeal gonorrhoea as defined by the WHO recommended cure rate of 95% or greater.[4] However, following widespread use of oral ESCs in Japan, gonococci with reduced susceptibility to these agents emerged in Japan in 2001 and were associated with cefixime treatment failures.[5-7]It was noted early on that, whilst these early strains were generally resistant to fluoroquinolones and penicillin, they remained susceptible to intramuscular ceftriaxone, albeit with raised ceftriaxone MICs compared to fully susceptible strains.[5]More worrying has been the recent emergence of XDR *N. gonorrhoeae* strains among CSW and MSM populations which are characterized by high ceftriaxone MICs.[8-10] The first such gonococcal strain (H041) possessed a ceftriaxone MIC of 2-4 mg/l and was isolated from the oro-pharynx of a Japanese female CSW in Kyoto in 2009.[8]

Current recommendations for dual drug therapy to avoid further escalation in ESC-resistant gonorrhoea

Both the US Centers for Disease Control and Prevention (CDC) and, in the UK, the British Association for Sexual health and HIV (BASHH) and Public Health England's Gonococcal Resistance to Antimicrobials Surveillance Programme (GRASP) Action Plan for England and Wales now recommend that gonorrhoea is treated with an injectable ceftriaxone [250mg USA; 500mg UK] and single dose oral azithromycin [1g] as first-line therapy.[11-14]Australia has also recommended dual therapy for gonorrhoea with the same regimen as is recommended in the UK (i.e. higher dose ceftriaxone and azithromycin).

Current situation regarding ESC-resistant gonorrhoea in South Africa

The syndromic management approach to treat gonorrhoea in the public sector makes it difficult to define the problem on a national level as samples are not taken for microbiological investigation and determination of gonococcal susceptibility profiles. To date, the limited surveillance that has been undertaken by the Centre for HIV and STIs at a small number of public sector primary healthcare clinics since 2007 suggests that gonococci are still susceptible in the populations accessing these clinics, which tend to be heterosexual and predominantly black African individuals with low income.[15]

The NICD, however, has received and confirmed the existence of four cefixime-resistant gonococci from Ampath Laboratories. These isolates came from the urethral pus of four white men-who-have-sex-with-men (MSM) who acquired their gonorrhoea in Johannesburg (n=3) and Cape Town (n=1).[16,17] One of these four men had a history of treatment failure with cefixime. These isolates were genetically identical by NG-MAST and MLST typing methods and appear to be part of a successful international clone that has been associated with cefixime treatment

failures in Asia, Europe and North America and have been associated with transmission networks involving MSM.[17] Historically, antimicrobial resistant gonorrhoea traditionally emerges as a clinical problem in high-risk core groups such as MSM and commercial sex workers before these strains spread into the general population through bridging.[18]
Accordingly, it almost inevitable that South Africa will face the emergence and spread of cefixime resistant gonorrhoea within the countries heterosexual population within the next 5 years unless action is taken now in order to try and slow down or arrest the emergence of these ESC-resistant strains through provision of dual therapy in the form of an ESC (either oral cefixime or intramuscular ceftriaxone) plus single dose azithromycin [1g]. Doxycycline is not a viable alternative to azithromycin to treat gonorrhoea as part of dual therapy as prolonged use of this antimicrobial agent in South Africa has resulted in a high prevalence (36-73%) of high-level doxycyclineresistant *N. gonorrhoeae* strains in Gauteng.[19,20]

Use of azithromycin at higher [2g] dose to treat suspected cefixime treatment failures

In the setting of STI syndromic management within South Africa's public healthcare system, it is not yet recommended to undertake laboratory-based antimicrobial susceptibility testing and, rather than lose such patients to follow-up, it should be recommended that suspected cefixime treatment failures receive prompt dual therapy with high dose intramuscular ceftriaxone [1g] and high singe oral dose azithromycin [2g]. The only alternative agent to give with the ceftriaxone would be intramuscular gentamicin but currently this is not available in primary health care clinics. Spectinomycin has been used in some settings but this drug is not available within South Africa. The early and effective treatment of patients with suspected ESC-resistant gonorrhoea is of great public health importance if one wishes to prevent transmission of such strains in the community.

Use of azithromycin to treat chlamydial infection

A systematic review and meta-analysis comparing azithromycin and doxycycline for the treatment of genital chlamydia was published by Lau and Qureshi in 2002.[21]Studies were identified by searching computerized English-language databases for the period 1975 to August 2001, supplemented by a manual bibliographic search. Criteria for inclusion were (1) randomized trial design; (2) regimens of oral doxycycline (100 mg twice daily for 7 days) and oral azithromycin (1 g once); (3) males >15 years of age and non-pregnant females >15 years of age; (4) and evaluation of microbial cure at follow-up. Data were extracted on diagnostic assay, follow-up time, study design, sponsorship, patients' characteristics, adverse events, attrition rates, and outcomes.Twelve trials met the inclusion criteria; 1543 patients were evaluated for microbial cure and 2171 for adverse events. Cure rates were 97% for azithromycin and 98% for doxycycline. Adverse events occurred in 25% and 23% of patients treated with azithromycin and doxycycline, respectively. After pooling of the data, differences in efficacy and risk were computed. The efficacy difference for microbial cure (0.01; 95% CI, -0.01-0.02) and the risk difference for adverse events (0.01; 95% CI, -0.02-0.04) between the two drugs were not statistically significant. The authors concluded that azithromycin and doxycycline were equally efficacious in achieving microbial cure and have similar tolerability.

Use of azithromycin to treat pelvic inflammatory disease (lower abdominal pain syndrome)

In the context of primary health care, the lower abdominal pain syndrome (LAP) (which is an alternative name of pelvic inflammatory disease (PID) in the STI syndromic approach) is typically mild and thus associated more with chlamydial infection than severe anaerobic infection or acute gonococcalPID, which are more likely to present to hospital settings. Traditionally, chlamydial PID is treated with a 14 day course of doxycycline [100mg 12-hourly] but gastrointestinal side effects may limit compliance. Compliance with drug therapy could be much improved and the azithromycin was given as directly observed single dose therapy. Clinical trial data is only available for the two dose approach (azithromycin 1g at initiation of treatment on repeated on week later).[22]Savaris*et al.* reported that azithromycin [1g] orally given once a week for 2 weeks has demonstrated effectiveness when used in combination with single dose intramuscular ceftriaxone [250mg].[22]Patients with mild PID received an intramuscular injection of 250mg of ceftriaxone, and were randomly assigned to receive 200mg/day of doxycycline for 2 weeks, or 1g of azithromycin per week, for 2 weeks. The degree of pain was assessed on days 2, 7, and 14 and clinical cure was assessed on day 14. From 133 patients eligible for the study, 13 were excluded for having conditions other than PID, 11 were lost on follow-up, and three had oral intolerance to the antibiotics, yielding 106 for protocol analysis. No significant difference was observed regarding the degree of pain between the doxycycline and azithromycin groups. Clinical cure per protocol was 98.2% (56 of 57; 95% confidence interval [CI], 0.9-0.99) with azithromycin, and 85.7% (42 of 49; 95% CI, 0.72-0.93) with doxycycline (P=0.02). In a modified intention to treat analysis, clinical cure was 90.3% (56 of 62; 95% CI, 0.80-0.96) with azithromycin, and 72.4% (42 of 58; 95% CI, 0.58-0.82) with doxycycline (P=.01); a relative risk of 0.35, and a number needed to treat of six for benefit with azithromycin. The authors concluded that, when combined with ceftriaxone, 1g of azithromycin weekly for 2 weeks is equivalent to ceftriaxone plus a 14-day course of doxycycline for treating mild PID.

The Primary Healthcare Expert ReviewCommittee recommended a single dose of azithromycin [1g] for LAP syndrome based on the fact that single dose therapy is adequate for eradication of*Chlamydia trachomatis* in other STI syndromes and because pharmacokinetic data has shown that therapeutic azithromycin concentrations are sustained in tissue and neutrophils for at least 10 days after single dose therapy. [23,24]The single dose azithromycin would need to be administered with single dose intramuscular ceftriaxone [250mg] to treat *N. gonorrhoeae* and any other Gram negative pathogens as well as a 7 day course of metronidazole [400mg 12-hourly] to cover anaerobic infection and bacterial vaginosis.

Use of azithromycin to treat epididymo-orchitis (scrotal swelling syndrome, SSW)

Analogous to discussions mentioned above for LAP, the Essential Drugs Programme's Primary Healthcare Committee used expert advice to recommend replacing a 2 weeks course of doxycycline (100mg 12-hourly) with a single oral dose of azithromycin [1g]. There is no relevant clinical trial data to support this decision but the pharmacokinetic properties of azithromycin suggest that this approach will treat the vast majority of SSW cases successfully. The single

dose azithromycin would need to be administered with single dose intramuscular ceftriaxone [250mg] to treat *N. gonorrhoeae* and any other Gram negative pathogens.

Use of azithromycin to treat *M. genitalium* infections

The topic of *Mycoplasma genitalium* is a complex issue as currently it is not regarded as a major cause of uro-genital pathology in the MUS and VDS syndromes managed at primary health care level in South Africa. *Mycoplasma genitalium* is a sexually transmitted pathogen, causing up to 25% of cases of non-gonococcal urethritis in men, and it is strongly associated with cervicitis and pelvic inflammatory disease in women, and possibly female infertility. Data are inconclusive regarding the role of *M. genitalium* in adverse pregnancy outcomes and ectopic pregnancy. Within South Africa, *M. genitalium* is detected at a prevalence of 2-8% in MUS cases and 3-9% in VDS cases in aetiological surveys conducted in several of South Africa's nine provinces (unpublished data, Centre for HIV and STIs, NICD/NHLS).

It is an extremely difficult organism to grow and only a small number of laboratories in developed countries are able to do this successfully. The detection of *M. genitalium* therefore relies on nucleic acid amplification techniques. The inability of most laboratories to culture the organism hampers attempts to define its antimicrobial susceptibility to drugs commonly used to treat urethritis and cervicitis. Some laboratories are predicting resistance phenotypes based on the presence of characteristic genetic correlates. Although there are no antimicrobial susceptibility data from Africa, data from Australia, Europe and North America suggests that a high prevalence of resistance to doxycycline exists.[25,26]Currently, the usual international first-line treatment is the macrolide antibiotic azithromycin, but an increasing incidence of treatment failure over the last 5 years suggests the emergence of antibiotic resistance possibly through use of single-dose azithromycin [1g] to treat chlamydial infections.[27] Studies have shown that a high proportion of M. genitalium infections are cured when azithromycin is given in a longer 5 day course.[28] The mutations responsible for macrolide resistance have been found in the 23S rRNA gene in numerous *M. genitalium*populations.[29,30] A second-line antibiotic, the fluoroquinolone, moxifloxacin, was thought to be a reliable alternative when azithromycin began to fail, but recent studies have identified mutations that may confer fluoroquinolone resistance in the genes *parC* and *gyrA*.[25,29,30]

Azithromycin as a treatment for chancroid and lymphogranulomavenereum (LGV)

Both chancroid and LGV are now very rare in South Africa and this has been hailed as one of the great successes of the syndromic management approach. Aetiological surveys conducted by the Centre for HIV and STIs at NICD in the past 3-5 years have shown that both conditions occur at a prevalence of 1% or less among patients with genital ulcer disease (GUD) (unpublished data, Centre for HIV and STIs, NICD/NHLS). In addition, reports of chancroid/LGV-associated buboes are much less common than 20 years ago. In the current national STI guidelines, a 7 day course of erythromycin [500mg 6-hourly] is included as part of first-line GUD treatment. However, this could be removed from first-line therapy and be replaced by a single oral dose of azithromycin [1g] at one week follow-up for those patients with GUD who are not improving. Expert opinion is that compliance with single dose azithromycin

with be greater than with the 6-hourly regimen for erythromycin. Azithromycin as a single dose is a recognized first-line treatment for chancroid in the guidelines of the WHO, CDC, UK (BASHH) and the European region and replacement of erythromycin with azithromycin would be in line with international expert opinion.[31]We lack treatment trials for the primary ulcerative stage of LGV but expert opinion would support the use of a single dose of azithromycin in the context of genital ulceration in the absence of a bubo.

Additional doses would be required to treat the LGV ano-rectal and inguinal syndromes that comprise the secondary stage. Some clinicians are currently using oral azithromycin 1g given at treatment initiation and repeated at day 7 and 14 to treat LGV proctitis in Europe (D. Lewis, personal communication). However, CDC and many other guidelines still recommend either a 21 days course of erythromycin [500mg 6-hourly] or a combination of 21 days of doxycycline [100mg 12-hourly, for LGV] plus 3 days of ciprofloxacin [500mg 12-hourly, for chancroid] on the basis that there are no randomized controlled trials using azithromycin to treat either LGV ano-rectal syndrome or inguinal buboes. Given the pharmacokinetic properties of azithromycin, the Primary Healthcare Expert Review Committee was of the opinion that two 1g doses of azithromycin given a week apart should provide ample therapy to treat inguinal buboes. Currently, there is not a syndrome for ano-rectal discharge and so the issue of LGV proctitis/proctocolitis was not discussed at the Committee on the basis that it would generally be managed by a doctor within primary care or at the hospital level.

Advantages and disadvantages of incorporating single dose azithromycin in STI treatment algorithms (most important issues bolded)

STI syndrome	Current drug	Advantage of switch to single dose azithomycin [1g] (repeated at 1 week for bubo)	Disadvantage of switch to single dose azithomycin [1g] (repeated at 1 week for bubo)
Male urethritis syndrome	Doxycyline 100mg 12-hrly x 7 days	• **Provides effective dual therapy for *N. gonorrhoeae* to slow down development of ESC resistant gonorrhoea** • Currently, >98% of gonococci tested in NICD surveys in South Africa are susceptible to azithromycin *in vitro* c.f. <30% of gonococci susceptible *in vitro* to doxycyline • **Single dose improves compliance and allows directly observed therapy by nurse** • Azithromycin 2g oral dose will be needed for manage suspected cefixime treatment failures in combination with high dose intramuscular ceftriaxone • More efficacious against *M. genitalium* than doxycycline • Not associated with photosensitivity and generally well tolerated	• May increase the prevalence of macrolide resistant *M. genitalium* • Increased cost c.f. doxycycline
Vaginal discharge syndrome (non-pregnant/non-breast feeding)	Doxycyline 100mg 12-hrly x 7 days	• **Provides effective dual therapy for *N. gonorrhoeae* to slow down development of ESC resistant gonorrhoea** • Currently, >98% of gonococci tested in NICD surveys in South Africa are susceptible to azithromycin *in vitro* c.f. <30% of gonococci susceptible *in vitro* to doxycyline • **Single dose improves compliance and allows directly observed therapy by nurse** • More efficacious against *M. genitalium* than doxycycline • Not associated with photosensitivity and generally well tolerated	• May increase the prevalence of macrolide resistant *M. genitalium* • Increased cost c.f. doxycycline
Vaginal discharge syndrome (pregnant/breast feeding)	Amoxycillin500mg 8-hrly x 7 days	• Same comments for gonorrhoea as above • **Allows same drug regimen for all women with vaginal discharge syndrome (removes risk of medico-legal issues arising frompprescribing of doxycycline to pregnant and breast-feeding women)** • **Single dose improves compliance and allows directly observed therapy by nurse**	• May increase the prevalence of macrolide resistant *M. genitalium* • May cause some nausea in pregnant women which can be avoided by ensuring azithromycin is taken after food • Increased cost c.f. amoxycillin

		• Has clinical activity again *M. genitalium*unlikeamoxycillin	
Scrotal swelling syndrome	Doxycyline 100mg 12-hrly x 14 days	• **Provides effective dual therapy for *N. gonorrhoeae* to slow down development of ESC resistant gonorrhoea** • Currently, >98% of gonococci tested in NICD surveys in South Africa are susceptible to azithromycin *in vitro* c.f. <30% of gonococci susceptible *in vitro* to doxycyline • **Single dose improves compliance and allows directly observed therapy by nurse** • More efficacious against *M. genitalium* than doxycycline • Not associated with photosensitivity and generally well tolerated	• Increased cost c.f. doxycycline • May have less anti-inflammatory activity than doxycycline but this can be overcome with use of ibuprofen • **No randomized controlled trials to support use of azithromycin in this syndrome – recommendation to switch would be based on expert opinion**
Lower abdominal pain syndrome (non-pregnant/non-breast feeding)	Doxycyline 100mg 12-hrly x 14 days	• **Provides effective dual therapy for *N. gonorrhoeae* to slow down development of ESC resistant gonorrhoea** • Currently, >98% of gonococci tested in NICD surveys in South Africa are susceptible to azithromycin *in vitro* c.f. <30% of gonococci susceptible *in vitro* to doxycyline • **Single dose improves compliance and allows directly observed therapy by nurse** • More efficacious against *M. genitalium* than doxycycline • Not associated with photosensitivity and generally well tolerated	• Increased cost c.f. doxycycline • **One randomized controlled trial to support use of azithromycin given as two single 1g doses given a week apart** • **No randomized controlled trials to support use of the single 1g dose of azithromycin in this syndrome – recommendation to switch would be based on expert opinion**
Genital ulcer syndrome	Erythromycin 500mg 6-hrly x 7 days	• **Single dose improves compliance and allows directly observed therapy by nurse** • Will now only be given as a second line therapy to patients with genital ulceration not responding to acyclovir and benzathine penicillin – this will reduce cost of treating this syndrome	• A small number of HIV-immunosuppressed patients may require a second treatment if chancroid is present – however, both chancroid and LGV are rare thesedays (each disease accounts for <1% of genital ulcers) • Increased cost c.f. erythromycin
Bubo	Erythromycin 500mg 6-hrly x 14 days	• **A 1g dose of azithromycin, repeated after a week at clinical review, improves compliance and allows directly observed therapy by nurse**	• Increased cost c.f. erythromycin

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