health
Department:
Health
REPUBLIC OF SOUTH AFRICA

2030 NDP

SOUTH AFRICAN PRIMARY HEALTHCARE LEVEL ESSENTIAL MEDICINES LIST
CHAPTER 12: SEXUALLY TRANSMITTED INFECTIONS
NEMLC RECOMMENDATIONS FOR MEDICINE AMENDMENTS (2016 -2018)

Medicine amendment recommendations, with supporting evidence and rationale are listed below. Kindly review the medicine amendments in the context of the dental and oral conditions chapter.

SECTION	MEDICINE/MANAEGEMENT	ADDED/DELETED/NOT ADDED/ AMENDED/ RETAINED
General		
– *Treatment of N. gonorrhoeae*	Cefixime, oral	Not added
	Ceftriaxone, IM	Retained
	Azithromycin, oral	Retained
12.1 Vaginal discharge syndrome (VDS)		
	Age cut-off criterion	Deleted from VDS algorithm
	Sexual activity criterion	Added to VDS algorithm
	Clotrimazole + metronidazole dual therapy	Amended to monotherapy directed syndromic management
	Speculum examination	Added to VDS algorithm to differentiate between cervicitis and vaginitis
	Clotrimazole, topical	Added
	Fluconazole, oral	Not added
12.2 Lower abdominal pain (LAP)		
– *Severely ill patients: Severe penicillin allergy*	Gentamicin, IV	Not added
	Clindamycin, IV	Not added
	Ciprofloxacin, oral	Not added
	Ceftriaxone, IV, 1 g	Retained
	Metronidazole, oral, 400mg	Retained
12.5 Genital ulcer syndrome (GUS)		
	Ceftriaxone, IM	Not added
	Benzathine benzylpenicillin, IM 2.4MU	Retained and amended
	Doxycycline, oral	Amended
– *Aciclovir-resistant ulcers*	Azithromycin, oral, 1 g	Retained and directions for use amended
12.6 Bubo		
	Azithromycin, oral, 1g	Dosing amended
12.7 Balanitis/balanoposthitis (BAL)		
	Benzathine benzylpenicillin, IM, 2.4MU	Deleted
12.8 Syphilis serology and treatment		
– *Early syphilis and Late latent syphilis treatment: Severe penicillin allergy and if benzathine benzylpenicillin is unavailable*	Doxycycline, oral	Added
– *Pregnant women*	Amoxicillin, oral	Added
	Probenicid, oral	Added
– *Serology testing*	RPR testing	Amended (i.e. Follow up serology for all syphilis cases treated with oral antibiotics)
12.10 Treatment of partners		
	Ceftriaxone, 250 mg, IM	Added
	Azithromycin, 1 g, oral	Added
	Metronidazole, 2g, oral	Added
	Doxcycyline, oral	Added

	Benzathine benzylpenicillin, IM 2.4 mu	Added
	Lidocaine 1% without epinephrine (adrenaline)	Added
12.13 Pubic lice		
– *Pediculosis of the eyelashes/ eyebrows*	Yellow petroleum jelly	Added
	White petroleum jelly	Deleted

Acknowledgement: National Institute Communicable Diseases.

GENERAL

Delineation of management of STIs according to level of care

Algorithms were amended to provide guidance at primary level of care. Further investigation and management of treatment-resistant cases to be done at secondary level; to be included in the Adult Hospital level STGs and EML, as currently management is guided by levels of care and relevant guidance should be included in the appropriate guidelines.

Level of Evidence: III Expert opinion

Causative pathogens for STI syndromes

The following summary was included in the STG to assist the healthcare worker:

ORGANISM	SYDROME/S	MEDICINE MANAGEMENT
Neisseria gonorrhoeae	VDS, MUS, LAP	ceftriaxone + azithromycin
Chlamydia trachomatis	VDS, MUS, LAP	azithromycin
Trichomonas vaginalis	VDS, LAP	metronidazole
Bacterial vaginosis (overgrowth of Gardnerella vaginalis, lactobacillus, anaerobes etc)	VDS	metronidazole
Candida albicans	VDS	clotrimazole
Treponema pallidum	GUS	doxycyline/benzathine penicillin
Herpes simplex	GUS	aciclovir
Haemophilus ducreyi	GUS	azithromycin

Point of care testing

Rapid diagnostic testing of STIs not currently being implemented by the NDoH STI Programme. The tests need to be validated for use in the clinic setting prior to national implementation; and a proficiency testing scheme must be developed for quality assurance of results at participating clinics.

Treatment of *Neisseria gonorrhoeae*

Cefixime, oral: *not added*
Ceftriaxone, IM: *retained*
Azithromycin, oral: *retained*

External motivation was received from Merck (Pty) Ltd, for cefixime + azithromycin for eradication of *Neisseria gonorrhoeae* in the syndromic management of vaginal discharge syndrome (VDS), male urethritis syndrome (MUS) and lower abdominal pain (LAP).

Multi-drug and extensively-drug resistant gonorrhoea: Historically, cefixime was recommended to treat *N. gonorrhoeae* due to widespread resistance to fluoroquinolones. However, in 2001, Japan[1] [2] reported

[1] Ito M et al. Remarkable increase in central Japan in 2001-2002 of Neisseria gonorrhoeae isolates with decreased susceptibility to penicillin, tetracycline, oral cephalosporins, and fluoroquinolones. Antimicrob Agents Chemother. 2004 Aug;48(8):3185-7. https://www.ncbi.nlm.nih.gov/pubmed/15273147

[2] Tanaka M, et al. A remarkable reduction in the susceptibility of Neisseria gonorrhoeae isolates to cephems and the selection of antibiotic regimens for the single-dose treatment of gonococcal infection in Japan. J Infect Chemother. 2002 Mar;8(1):81-6. https://www.ncbi.nlm.nih.gov/pubmed/11957125

cefixime treatment failures (including extended cefixime regimens)[3], that were susceptible to ceftriaxone. Locally, NICD[4] [5] received reports of 4 cefixime treatment failure cases. These isolates were laboratory confirmed to be resistant to cefixime and susceptible to ceftriaxone. And, in 2014 ceftriaxone, IM was recommended as dual therapy with azithromycin for syndromic management of STIs.[6]

Ceftriaxone PK/PD: It was reported that ceftriaxone's more favourable pharmacokinetic/ pharmacodynamics (PK/PD) profile compared with cefixime would probably result in greater bacteriological activity leading to better cure rate than cefixime and reduce the risk of the emergence of resistance.[7] Ceftriaxone also has greater affinity than cefixime for the mosaic penicillin-binding protein 2 that confers resistance to extended spectrum cephalosporins.[8] Ceftriaxone MICs are generally lower than cefixime for *N. gonorrhoeae*.[9]

Comparative prices (direct medicine prices): Replacing cefixime with ceftriaxone + lidocaine 1% would result in additional costs incurred.

Medicine	Price	Data source
Cefixime, oral, 400 mg tablet	**R 15.00**	Merck (Pty) Ltd quote, 20 December 2017.[10]
Ceftriaxone, IM, 250 mg diluted in 0.9 mL lidocaine 1%:	**R 12.35**	
Treatment regimen components:		
• *Ceftriaxone, 250 mg*	*R 3.67*	Contract circular RT301-2017
• *Lidocaine 1% without lidocaine, 0.9 mL (including 10% for wastage = 1 mL in total)*[11]	*R 0.44*	Contract circular HP06-2017SVP
• *Syringe and webcol*	*R 2.00*	
• *Clinical nurse practitioner time (2 minutes)*[12]	*R 6.24*	DPSA, OSD scale, April 2017

Note: Costs for antimicrobial resistance requiring additional susceptibility laboratory tests and up referral to secondary level of care for further management was not considered.

Recommendation: Ceftriaxone, IM be retained as the cephalosporin of choice as part of presumptive dual therapy for sexually transmitted infections.

Rationale: Antimicrobial resistant reports of *Neisseria gonorrhoeae* to cefixime globally and locally, greater affinity of ceftriaxone to causative organism warrants recommendation of ceftriaxone, IM. In addition, ceftriaxone, IM is cheaper than cefixime, oral.

Level of Evidence: III Case reports, Antimicrobial susceptibility study, Expert opinion

12.1 VAGINAL DISCHARGE SYNDROME (VDS)

Age cut-off criterion: *deleted from VDS algorithm*
Sexual activity criterion: *added to VDS algorithm*
Cotrimazole+metronidazole dual therapy: *amended to monotherapy directed syndromic management*

[3] Yokoi S,et al.. Threat to cefixime treatment for gonorrhea. Emerg Infect Dis. 2007 Aug;13(8):1275-7. https://www.ncbi.nlm.nih.gov/pubmed/17953118
[4] Lewis DA, et al. Phenotypic and genetic characterization of the first two cases of extended-spectrum-cephalosporin-resistant Neisseria gonorrhoeae infection in South Africa and association with cefixime treatment failure. J Antimicrob Chemother. 2013 Jun;68(6):1267-70. https://www.ncbi.nlm.nih.gov/pubmed/23416957
[5] Lewis DA. Gonorrhoea resistance among men who have sex with men: what's oral sex got to do with it? South Afr J Epidemiol Infect 2013;28(2):77. https://journals.co.za/content/mp_sajei/28/2/EJC138699
[6] PHC STGs and EML, 2014
[7] Chisholm SA, et al. Cephalosporin MIC creep among gonococci: time for a pharmacodynamic rethink? J AntimicrobChemother. 2010 Oct;65(10):2141-8. https://www.ncbi.nlm.nih.gov/pubmed/20693173
[8] Zhao S, Duncan M, Tomberg J, Davies C, Unemo M, Nicholas RA. Genetics of chromosomally mediated intermediate resistance to ceftriaxone and cefixime in Neisseria gonorrhoeae. Antimicrob Agents Chemother. 2009 Sep;53(9):3744-51. https://www.ncbi.nlm.nih.gov/pubmed/19528266
[9] Unemo M, Nicholas RA. Emergence of multidrug-resistant, extensively drug-resistant and untreatable gonorrhea. Future Microbiol. 2012 Dec;7(12):1401-22. https://www.ncbi.nlm.nih.gov/pubmed/23231489
[10] Data on file at NDoH, EDP.
[11] Contract circular HP062017SVP: Lidocaine 1% 20 mL = R 8.71.
[12] Department of Public Service and Administration. Occupation Specific Dispensations Scales, Aril 2017: Clinical Nurse Practitioner (Grade 1) – annual salary of R 394,665.00; assuming 42-hour week (2184 hours/annum) and that it takes an additional minute and a half to administer ceftriaxone IM, 250 mg vs directly observed treatment of cefixime, oral = R 4.52 for 1.5 minutes.

Speculum examination: *added to VDS algorithm to differentiate between cervicitis and vaginitis*

A: AGE CUT-OFF CRITERION

Previous age cut-off (<35 years) criterion: Unpublished surveillance data for VDS at Alexander Health Centre, Gauteng (2007 -2012) shared by NICD: Centre for STI and HIV informed the age cut-off criterion of < 35 years of age. In that survey, N gonorrhoea and C trachomatis were infrequent causes of VDS women > 35 years of age.

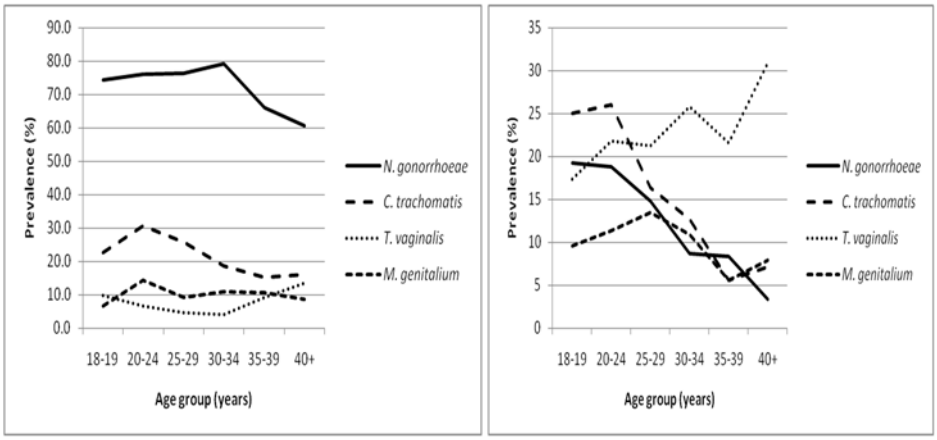


Figure 1a: Men **Figure 1b: Women**

Figure 1a & 1 b: Prevalence of *Neisseria gonorrhoeae*, *Chlamydia trachomatis, Trichomoniais vaginalis and Mycoplasma genitalium*by age group for men (n=1,218) and women (n=1,232) with genital discharges - combined survey data from six annual surveys undertaken from January to April each year in Alexandra Health Centre, 2007-2012.

Surveillance data for period 2015-2016 (Alexandra Health Centre): Surveillance data of women presenting with VDS at Alexandra Health Centre(n=771) for the period January 2015 to September 2016 provided by NICD/NHLS, stratified in 4 groups showed the following % of women > 35 years of age:

1. Bacterial vaginosis or candidiasis and no STI co-infection: 20%
2. Bacterial vaginosis or candidiasis and STI co-infection: 14%
3. STI infection only: 19%
4. No pathogens detected: 29%

National Surveillance data: The PHC 2014 VDS algorithm does not included treatment for gonorrhoea/chlamydia for women older than 35. However, local surveillance data from the 2014-2015 National Aetiological Surveillance (NAS) study (n=801)[13] shows that the median age of women with non-STI causes (BV/ Candidiasis) of VDS was 29 years (IQR 24 to 36); n=271, whereas that of women harbouring one or more STI pathogens was 26 years (IQR 22 to 34), n=87; the difference was not statistically significant (p=0.095) (801 VDS cases tested).

Accuracy of using age to determine STI aetiology: Sub-analysis of the national aetiology sentinel (NAS) surveillance data (April 2014 – September 2015) suggests that the overall accuracy (area under the ROC curve) of using age to predict presence of GC/CT infections was only 66.2% (95% CI 61.6 to 70.7%). Details of this analysis, using data from the NAS survey and provided by NICD (embargoed, to be published) appear in the table and figure below:

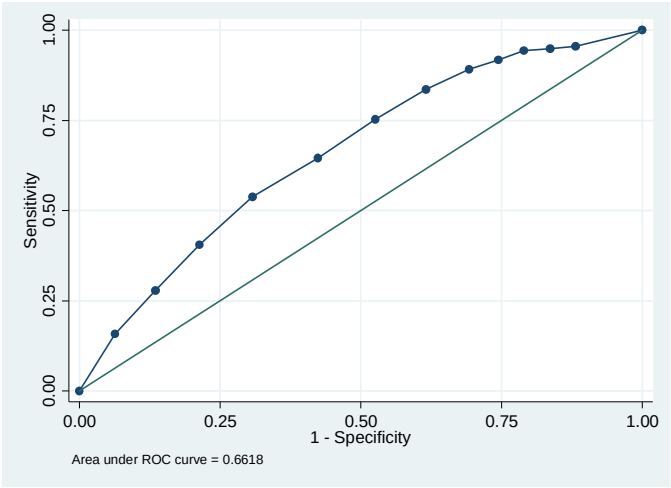
[13] National Institute for Communicable Diseases. Report on the Sentinel Surveillance of Sexually Transmitted Infection Syndrome Aetiologies and HPV Genotypes among Patients attending Public Health Facilities in South Africa (April 2014 – September 2015), embargoed, to be published.

Performance of different age cut offs for diagnosis of GC/CT infections

Age cut offs	Sensitivity of picking up GC/CT (%)	Specificity of picking up GC/CT (%)	Correctly classified (%)
>=50	100	0.0	20.9
47 - 49	95.6	11.9	29.3
44 - 46	94.9	16.4	32.8
41 - 43	94.3	21.0	36.3
38 - 40	91.8	25.5	39.4
35 - 37	89.2	30.7	42.9
32 - 34	83.5	38.4	47.8
29 - 31	75.3	47.4	53.2
26 - 28	64.6	57.6	59.1
24 - 25	53.8	69.3	66.1
22 - 23	40.5	78.6	70.7
20 - 21	27.9	86.5	74.2
18 - 20	15.8	97.8	77.4

Overall accuracy of using age for determining GC/CT infections = 66.2% (95% CI 61.6- 70.7%)

ROC curve for performance of increasing age in determining GC/CT infections



A ROC curve demonstrates several things:

1. It shows the trade-off between sensitivity and specificity (any increase in sensitivity will be accompanied by a decrease in specificity).
2. The closer the curve follows the left-hand border and then the top border of the ROC space, the more accurate the test.
3. The closer the curve comes to the 45-degree diagonal of the ROC space, the less accurate the test.
4. The area under the curve is a measure of test accuracy.

B: SEXUAL ACTIVITY AS A CRITERION:

Sexual risk behaviour: The local NAS surveillance data[14] showed that condom use at the last sexual encounter showed no significant difference between the group infected with STIs (42.4%) *vs.* not infected with STIs (36.7%); Sexual partner from another province in the last 3 months showed no significant difference between the groups (11.6% vs. 9.3%); Sexual partner from another country in the last 3 months showed no significant difference (7.0% vs. 6.6%); History of any STI syndrome in last 12 months, 43% vs. 47%, respectively, no significant difference.

Rational antibiotic use: The National surveillance survey did not stratify according to recent sexual activity. (The GERMSA survey will hopefully provide such data in the near future). However, the PHC Committee was of the opinion that using a history of recent sexual activity (within the past 3 months as a criterion for including treatment for STI pathogens in the treatment regimen for women presenting with VDS was more logical and biologically plausible than the previous age criterion, and would probably avoid inappropriate

[14]National Institute for Communicable Diseases. Report on the Sentinel Surveillance of Sexually Transmitted Infection Syndrome Aetiologies and HPV Genotypes among Patients attending Public Health Facilities in South Africa (April 2014 – September 2015), embargoed, to be published.

over-treatment of VDS cases with azithromycin+ceftriaxone. Thus, the STG recommends history of recent sexual activity as the major criterion for presumptive STI treatment.

C: VDS ALGORITHMS DIFFERENTIATES CLINICALLY BETWEEN CANDIDIASIS ANDBACTERIAL VAGINOSIS:
Previous dual therapy (metronidazole+cotrimazole): In the 2014 PHC VDS algorithm women >35 years were treated with both clotrimazole and metronidazole to cover candidiasis, bacterial vaginosis and trichomonas. Clinical features of vaginal candidiasis were not included in the algorithm.

Co-infection: Co-infection with candida (CA) (necessitating clotrimazole treatment) and bacterial vaginosis (BV) (necessitating metronidazole treatment) is rare. In local surveillance data from the NAS study (2014-2015)[15], only 5% of patients (40/801 of VDS cases) had BV **plus** CA (without STI)."The negative association between BV and vulvovaginal candidiasis has been attributed to an alteration of vaginal pH in BV, which creates an unfavourable environment for candida colonization and co-infection".

D: SPECULUM EXAMINATION:
Speculum examination for all women presenting with VDS is recommended by the STI Programme[16] to differentiate between cervicitis and vaginitis, especially in sexually active women, to limit unnecessary treatment for gonorrhoea and chlamydia. Speculae are available at primary care level facilities. The PHC Committee was of the opinion that compulsory speculum examinations for all women presenting with VDS are probably not feasible. There is a note under both VDS algorithms that speculum examinations should be done in all cases, but lack of speculum examination does not preclude treatment. However, the PHC Committee recommended that speculum examination should be done if symptoms persist after treatment for BV, in order to identify those women who should receive STI treatment.

Recommendations:
A. Age be removed as a criterion for treating chlamydia and gonococcal infections versus bacterial vaginosis.
B. Sexual activity be added as a criterion for syndromic treatment of STI when presenting with VDS.
C. The VDS algorithm(s) differentiate clinically between candidiasis and bacterial vaginosis.
D. Speculum examination be included to distinguish between cervicitis and vaginitis, in those women with persistent symptoms after treatment for BV.

Rationale:
- Local surveillance data from the National Aetiological Surveillance (NAS) study (2014-2015) showed that age was not a good predictor of infection with STI pathogens in women with VDS. The survey did not ask women about sexual activity, so the sexual activity as a predictor could not be assessed. However, the PHC Committee was of the opinion that the latter criterion was more logical and biologically plausible.
- Local surveillance data from the NAS study (2014-2015) showed that of the 801 VDS cases, only 4.5% had STI and candidiasis co-infection.
- Speculum examination to distinguish vaginitis and cervicitis, may guide appropriate antibiotic treatment with metronidazole (7 day course) or ceftriaxone + azithromycin, respectively. Speculum examination is recommended in the NDoH STI Programme's Comprehensive STI Clinical Management Guidelines (currently in draft format).

Level of Evidence: III Surveillance data, Guidelines, Expert opinion.
Review indicator: New evidence of association between sexual activity and infection with STI pathogens in women presenting with VDS.

[15]National Institute for Communicable Diseases. Report on the Sentinel Surveillance of Sexually Transmitted Infection Syndrome Aetiologies and HPV Genotypes among Patients attending Public Health Facilities in South Africa (April 2014 – September 2015), embargoed, to be published.
[16]NDoH: Comprehensive STI Clinical Management Guidelines, draft version.

Fluconazole, oral*: not added*
fluconazole was not pragmatic for treating candidiasis that is not responsive to clotrimazole, topical/per vagina at primary level of care. Usage creep and hepatotoxicity associated with fluconazole are concerns.
Level of Evidence: III Expert opinion

Clotrimazole, topical: *added*
VDS algorithm recommends clotrimazole cream topically if prominent vulval symptoms are present (Clotrimazole, topical was in the 2008 VDS algorithm, removed from the 2014 version and recommended for re-inclusion in the updated VDS algorithm).
Level of Evidence: III Expert opinion

Referral

Recommendation: Patients failing treatment as indicated in the VDS algorithm must be referred. Their management to be included in the updated Adult Hospital Level STG.
Rationale: Specimens must be sent for specific antibiotic susceptibility tests at secondary level of care, if there is treatment failure at primary level of care.
Level of Evidence: III Expert opinion

12.2 LOWER ABDOMINAL PAIN (LAP)

Severely ill patients: Severe penicillin allergy
Gentamicin, IV: *not added*
Clindamycin, IV: *not added*
Ciprofloxacin, oral: *not added*
Ceftriaxone, IV, 1 g: *retained*
Metronidazole, oral, 400mg: *retained*

Gentamicin, IV, clindamycin, IV and ciprofloxacin, oral not recommended for severe penicillin allergic patients as a single dose prior to referral to secondary level of care.
Rationale: This is a single pre-referral dose and primary healthcare workers are trained in the management of anaphylaxis with relevant medicines available on emergency trolleys. Not pragmatic to add gentamicin IV, clindamycin, IV and ciprofloxacin, oral to the PHC EML for a single indication, which was possibly uncommon.
Level of Evidence: III Expert opinion

12.5 GENITAL ULCER SYNDROME (GUS)

Ceftriaxone, IM: *not added*
Limited evidence is available. A network meta-analysis of RCTs and observational studies[17] suggested that ceftriaxone may be effective as penicillin for treatment of syphilis (treatment failure of penicillin compared to ceftriaxone: RR 0.92, 95% CI 0.12 to 6.93, p= 0.992). However, this analysis was not powered to demonstrate equivalence (3 small RCTs with 30 participants in total were reviewed). Additional limitations included heterogeneity of studies: varied treatment regimens, different syphilis stages and outcomes (treatment failure vs reinfection). High-quality, large-scale RCTs are needed to verify the efficacy of ceftriaxone in treating early syphilis.
Recommendation: Ceftriaxone, IM, not be recommended for treatment of early syphilis.
Rationale: Insufficient evidence of efficacy for ceftriaxone to treat early syphilis.
Level of Evidence: II Systematic review of low quality studies

[17] Liu HY, Han Y, Chen XS, Bai L, Guo SP, Li L, Wu P, Yin YP. Comparison of efficacy of treatments for early syphilis: A systematic review and network meta-analysis of randomized controlled trials and observational studies. PLoS One. 2017 Jun 28;12(6):e0180001.

Benzathine benzylpenicillin, IM: *deleted*
Doxycyline, oral: *added*
Due to the global shortage of benzathine benzylpenicllin (limited global supply of the active pharmaceutical ingredient) doxycyline, oral is recommended for syndromic management of genital ulcers, except in pregnancy. Benzathine benzylpenicillin is the recommended treatment for syphilis in neonates and pregnant women. In pregnancy, azithromycin does not effectively treat syphilis in the foetus, and resistance develops rapidly to macrolides (e.g. azithromycin).
In addition, chancroid is not common.
Level of Evidence: III Guidelines[18]

Pregnant women
Recommendation that pregnant women presenting with genital ulcer(s) in third trimester should be referred was included in the algorithm due to the risk of neonatal herpes, aligned with the NDoH Maternity Care Guidelines[19].
Level of Evidence: III Guidelines

Aciclovir-resistant ulcers
Azithromycin, oral, 1 g: *retained and directions for use amended*
Although, *Haemophilus ducreyi*is uncommon[20], the PHC ERC was of the opinion that presumptive treatment with azithromycin should be provided at PHC level of care, to cover the few cases that may occur. However, for pragmatic reasons, failure of azithromycin treatment requiring referral to secondary level of care for further pathology tests was amended from "*48 hours*" to "*7 days*".
Recommendation: Presumptive therapy for *Haemophilus ducreyii,* as single dose azithromycin be retained at primary level of care. Failure of therapy requiring referral to be assessed after 7 days, as oppose to 48 hours.
*Rationale: Haemophilus ducreyi*is uncommon, but presumptive therapy may cover the few cases that may present at primary level of care.
Level of Evidence: III Surveillance data, Expert opinion

NEMLC MEETING DISCUSSION: 2 NOVEMBER 2017

NEMLC Recommendations:
- GUS algorithm be updated replacing benzathine benzylpenicillin with doxycycline, except in pregnancy, due to the current global supply challenges.
- The foreword of the STI chapter provides information explaining the substitution of benzathine benzylpenicillin with doxycyline.
- The PHC Committee review the evidence for amoxicillin+probenicid for treatment of syphilis, for tabling at a follow-up NEMLC meeting.

12.6 BUBO

Azithromycin, oral, 1g: *dosing amended*
Azithromycin treatment amended for a period of 3 weeks, rather than 2 weeks as described in a surveillance study[21].Both recommendations are based on level 3 evidence; pharmacokinetic data and guidelines, respectively.

[18]World Health Organization. WHO guidelines for the treatment of Treponema pallidum (syphilis), 2016. http://apps.who.int/iris/bitstream/10665/249572/1/9789241549806-eng.pdf
[19] NDoH Maternity Care Guidelines, 2016.
[20]González-Beiras C, Marks M, Chen CY, Roberts S, Mitjà O. Epidemiology of Haemophilus ducreyi Infections. Emerg Infect Dis. 2016 Jan;22(1):1-8
- *surveillance data reported 2 isolates of Haemophilus ducreyi and 1 isolate of Lymphogranuloma venereum (n=171specimens)*
[21]Hill SC, Hodson L, Smith A. An audit on the management of lymphogranuloma venereum in a sexual health clinic in London, UK.Int J STD AIDS. 2010 Nov;21(11):772-6.

Recommendation: Update weekly azithromycin, 1 g, oral to a period of 3 weeks.
Rationale: Aligned with Infectious Diseases Society of America Guidelines: *Lymphogranuloma venereum* 2015: Clinical Presentation, Diagnosis, and Treatment.[22]
Level of Evidence: III Surveillance study, Guidelines

12.7 BALANITIS/BALANOPOSTHITIS (BAL)

Benzathine benzylpenicillin, IM, 2.4MU: *deleted*
Syphilitic balanitis is very rare[23][24][25] and management with benzathine benzylpenicillin was removed from the BAL algorithm.
Recommendation: Benzathine benzylpenicillin removed from the BAL algorithm.
Rationale: Syphilitic balanitis reported to be rare.
Level of Evidence: III Guidelines[26]

12.8 SYPHILIS SEROLOGY AND TREATMENT

Early syphilis treatment
Doxycycline, oral: *amended to include indication "if benzathine benzylpenicillin is unavailable"*
Rationale: There is a continuous supply challenge with benzathine benzylpenicillin. Thus, use of this agent requires to be restricted further; as currently only this agent is available for use in syphilis in pregnancy. WHO guidelines for the treatment of *Treponema pallidum* (syphilis), 2016 recommends doxycycline as an alternative option.
Level of Evidence: III Guidelines[27]

Late latent syphilis treatment
Severe penicillin allergy or if benzathine benzylpenicillin is unavailable:
Doxycycline, oral: *added*
Rationale: Management in patients with severe penicillin allergy aligned with the WHO guidelines for the treatment of *Treponema pallidum* (syphilis), 2016.
Level of Evidence: III Guidelines[28]

Pregnant women
Amoxicillin, oral: *added*
Probenicid, oral: *added*
Refer to the medicine review: Amoxicillin + probenecid for syphilis in pregnant women, January 2018, for detailed information.

Amoxicillin+Proben
icid_Syphilis in preg

[22] Stoner BP, Cohen SE. Lymphogranuloma Venereum 2015: Clinical Presentation, Diagnosis, and Treatment. Clin Infect Dis. 2015 Dec 15;61Suppl 8:S865-73.
[23] - Abdennader S, Janier M, Morel P. Syphilitic balanitis of Follmann: three case reports. Acta DermVenereol. 2011 Mar;91(2):191-2.
[24]Mainetti C, Scolari F, Lautenschlager S. The clinical spectrum of syphilitic balanitis of Follmann: report of five cases and a review of the literature. J EurAcadDermatolVenereol. 2016 Oct;30(10):1810-1813.
[25]Korta DZ, Lewin JM, Patel RR, Sanchez M. Acute Syphilitic Balanitis and Gross Penile Edema in an HIVInfected Man. Global Journal of Dermatology & Venereology. 2013;1:18-20.
[26]Edwards SK, Bunker CB, Ziller F, van der Meijden WI.2013 European guideline for the management of balanoposthitis.Int J STD AIDS. 2014 Aug;25(9):615-26.
[27]World Health Organization. WHO guidelines for the treatment of Treponema pallidum (syphilis), 2016. http://apps.who.int/iris/bitstream/10665/249572/1/9789241549806-eng.pdf
[28]World Health Organization. WHO guidelines for the treatment of Treponema pallidum (syphilis), 2016. http://apps.who.int/iris/bitstream/10665/249572/1/9789241549806-eng.pdf

Recommendation: The Primary Health Care Committee recommended that amoxicillin plus probenecid to be included as an alternative if benzathine penicillin unavailable, for treatment of syphilis in pregnancy. RPR follow up recommended for all patients treated with this regimen, as tolerability and adherence may be problematic and there is little published data in pregnancy with this regimen.

Rationale: Due to long-term supply challenges of benzathine penicillin, doxycycline, an alternative option, should be avoided in pregnancy. A retrospective observational study[29] showed that amoxicillin+probenecid was effective in treating syphilis, with a 4-fold decrease in RPR titer reduction compared to no treatment.

Level of Evidence: III Observational Strudy

NEMLC MEETING DISCUSSION, 1 FEBRUARY 2018:

- **Amoxicillin + probenecid:**
  Pragmatic implications: The NEMLC was of the opinion that stocking probenecid at every PHC facility in the event that benzathine benzylpenicllin was unavailable (through normal procurement processes or S21 approval) was not considered to be pragmatic.
  NEMLC Recommendation: Prescribing of amoxicillin + probenecid for management of syphilis in pregnant women, when there is a stock-out of benzathine benzylpenicillin be restricted to doctors only (thereby limiting the number of facilities that could access amoxicillin + probenecid).
  Rationale: Limited indication of amoxicillin + probenecid for management of syphilis in pregnant women, when there is a stock-out of benzathine benzylpenicillin warrants restrictive measures to prevent wastage.
  Level of Evidence: III Expert opinion

Syphilis serology

RPR testing: *amended*

Evidence suggests that doxycyline is as efficacious as benzathine penicillin for the treatment of early syphilis, and there is no significant difference in treatment outcomes. [30] [31] [32]Therefore, monitoring for RPR serological response is unnecessary in doxycycline-treated patients. Testing for serological response in early syphilis should be done at least 6 months after appropriate therapy, therefore long-term follow-up of RPR is impractical at primary level.

Recommendation: Follow-up RPR testing 6 months after doxycycline treatment removed form syphilis treatment algorithm.

Rationale: Serological response rate of doxcycyline shown to be comparable to penicillin for the management of early syphilis.

Level of Evidence: II Systematic review of RCTS and observational studies, Observational studies, Expert opinion

NEMLC MEETING DISCUSSION, 1 FEBRUARY 2018:

- **Amoxicillin + probenecid:**
  Pragmatic implications: The NEMLC was of the opinion that stocking probenecid at every PHC facility in the event that benzathine benzylpenicllin was unavailable (through normal procurement processes or S21 approval) was not considered to be pragmatic.

[29] Tanizaki R, Nishijima T, Aoki T, Teruya K, Kikuchi Y, Oka S, et al. High-dose oral amoxicillin plus probenecid is highly effective for syphilis in patients with HIV infection. Clin Infect Dis. 2015;61(2):177-83. https://www.ncbi.nlm.nih.gov/pubmed/25829004

[30] Liu HY, Han Y, Chen XS, Bai L, Guo SP, Li L, Wu P, Yin YP. Comparison of efficacy of treatments for early syphilis: A systematic review and network meta-analysis of randomized controlled trials and observational studies. PLoS One. 2017 Jun 28;12(6):e0180001. https://www.ncbi.nlm.nih.gov/pubmed/28658325

[31] Salado-Rasmussen K, Hoffmann S, Cowan S, Jensen JS, Benfield T, Gerstoft J, Katzenstein TL. Serological Response to Treatment of Syphilis with Doxycycline Compared with Penicillin in HIV-infected Individuals. Acta Derm Venereol. 2016 Aug 23;96(6):807-11. https://www.ncbi.nlm.nih.gov/pubmed/26568359

[32] Dai T, Qu R, Liu J, Zhou P, Wang Q. Efficacy of Doxycycline in the Treatment of Syphilis. Antimicrob Agents Chemother. 2016 Dec 27;61(1). pii: e01092-16. https://www.ncbi.nlm.nih.gov/pubmed/27795370

NEMLC Recommendation: Prescribing of amoxicillin + probenecid for management of syphilis in pregnant women, when there is a stock-out of benzathine benzylpenicillin be restricted to doctors only (thereby limiting the number of facilities that could access amoxicillin + probenecid).
Rationale: Limited indication of amoxicillin + probenecid for management of syphilis in pregnant women, when there is a stock-out of benzathine benzylpenicillin warrants restrictive measures to prevent wastage.
Level of Evidence: III Expert opinion

12.10 TREATMENT OF PARTNERS

Ceftriaxone, 250 mg, IM: *added*
Azithromycin, 1 g, oral: *added*
Metronidazole, 2g, oral: *added*
Doxycyline, oral: *added*
Benzathine benzylpenicillin, IM 2.4MU: *added*
Lidocaine 1% without epinephrine (adrenaline): *added*

The following treatment regimens were included in the STI chapter for treatment of partners (refer to the STI chapter for detailed information).

Syndrome	Asymptomatic Partner	Symptomatic partner
VDS	Ceftriaxone + azithromycin + metronidazole	Ceftriaxone + azithromycin + metronidazole PLUS treatment for syndrome present if not included in the above
LAP	Ceftriaxone + azithromycin + metronidazole	Ceftriaxone + azithromycin + metronidazole PLUS treatment for syndrome present if not included in the above
MUS	Ceftriaxone + azithromycin	Ceftriaxone + azithromycin PLUS treatment for syndrome present if not included in the above
Scrotal swelling	Ceftriaxone + azithromycin	Ceftriaxone + azithromycin PLUS treatment for syndrome present if not included in the above
GUS	Benzathine penicillin	Doxycycline/benzathine penicillin PLUS treatment for syndrome present if not included in the above
Bubo	Azithromycin	Azithromycin PLUS treatment for syndrome present if not included in the above

Aligned with the Centers for Disease Control and Prevention (CDC) Sexually Transmitted Diseases Treatment Guidelines, 2015[33].
Level of Evidence: III Guidelines

12.13 PUBIC LICE (PL)

Pediculosis of the eyelashes or eyebrows
Yellow petroleum jelly: *added*
White petroleum jelly: *not added*
White petroleum jelly should not be used near the eyes.
Level of Evidence: III Expert opinion

[33]Centers for Disease Control and Prevention. 2015 Sexually Transmitted Diseases Treatment Guidelines. https://www.cdc.gov/std/tg2015/