



health

Department:
Health
REPUBLIC OF SOUTH AFRICA



South Africa National Essential Medicine List Primary Healthcare Medication Review Process Component: Sexually transmitted infections

MEDICINE REVIEW

1. Executive Summary

Date: 15 January 2018
Medicine (INN): Amoxicillin, probenecid
Medicine (ATC): J01CA04, M04AB01
Indication (ICD10 code): A53.9
Patient population: Pregnant women with syphilis
Prevalence of condition: Unknown
Level of Care: Primary care
Prescriber Level: Nurses
Current standard of Care: Benzathine benzylpenicillin
Efficacy estimates: (preferably NNT) n/a
Motivator/reviewer name(s): Karen Cohen
PTC affiliation: Western Cape Provincial PTC

2. Name of author(s)/motivator(s)

Karen Cohen

3. Author affiliation and conflict of interest details

University of Cape Town; Member of the Primary Health Care Committee (2016-2018); No conflict of interest to declare.

4. Introduction/ Background

There is an ongoing shortage of benzathine penicillin. Doxycycline is being used as an alternative, but is contraindicated in pregnancy

5. Purpose/Objective i.e. PICO question [comparison to current standard of care for a specific indication]:

- P (*patient/population*): Patients with syphilis- all stages
- I (*intervention*): Amoxicillin plus probenecid
- C (*comparator*): Benzathine penicillin OR doxycycline
- O (*outcome*): Cure of syphilis- RPR decrease

6. Methods:

- a. **Data sources:** *Pubmed*
- b. **Search strategy**

Search was performed on 6 November 2017. Search terms: amoxicillin AND probenecid AND syphilis. 12 hits- see attached appendix 1.

- 1 retrospective observational study, 286 HIV infected men with syphilis(1) (Taniziki et al CID 2015. PMID 25829004)

c. Excluded studies:

- Case reports
 - 2 cases of syphilis in pregnancy successfully treated with A + P; 1 with ceftriaxone in addition(2). Katanami et al, Emerg Inf Disease 2017, PMID 28418316)
- 2 Case series describing drug concentrations, no clinical outcomes reported, no comparator:
 - 17 patients with neurosyphilis treated with amoxicillin 2g 3 times daily plus probenecid 500 mg 2 times daily- concentrations greater than 0.11g/L in CSF (treponemicidal)(3). (Morrison et al genitourin Med 1985 PMID 3910544)
 - 7 patients with various stages treated with amoxicillin 6g daily and probenecid 2g daily- achieved treponemicidal concentrations(4). (Faber et al Sex Transm Dis 1983. PMID 6359492- only abstract reviewed- could not access full text)

d. Evidence synthesis

<i>Author, date</i>	<i>Type of study</i>	<i>n</i>	<i>Population</i>	<i>Comparators</i>	<i>Primary outcome</i>	<i>Effect sizes</i>	<i>Comments</i>
Tanizaki 2015	Retrospective observational study	286	HIV infected men with syphilis	None	4 fold decrease in RPR titer	Efficacy 95.5% (95% CI 92.4 to 97.7%)	Retrospective; no comparator group

No comparative studies found addressing the PICO.

One retrospective study from Japan: 199 (69.6%) HIV infected men with syphilis(1). Patients were categorized as early syphilis (primary, secondary, and early latent syphilis) and 87 (30.4%) as late syphilis (late latent syphilis and syphilis of unknown duration). “Primary syphilis, secondary syphilis, early latent syphilis, late latent syphilis, and syphilis with unknown duration were diagnosed in 16 (5.6%), 146 (51.0%), 37 (12.9%), 21 (7.3%), and 66 (23.1%) patients, respectively.”

Amoxicillin 3g per day; range of dosing regimens. Majority (80.8%) received 3 times daily amoxicillin, 60.1% received 750 mg probenecid per day.

Adverse events in 28 subjects (9.8%): Skin rash in 21, fever in 9, diarrhoea in 2, elevated liver enzymes in 1.

21 (7.3%) switched to doxycycline due to side effects.

e. Evidence quality:

Low quality evidence. One retrospective observational study. Population HIV infected men.

7. Alternative agents:

None. Benzathine penicillin currently used, but there are ongoing shortages.

EVIDENCE TO DECISION FRAMEWORK

	JUDGEMENT	SUPPORTING EVIDENCE & ADDITIONAL CONSIDERATIONS
QUALITY OF EVIDENCE	<p>What is the overall confidence in the evidence of effectiveness?</p> <p>Confident Not confident Uncertain</p> <p><input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/></p>	Low quality evidence. No alternatives available
BENEFITS & HARMS	<p>Do the desirable effects outweigh the undesirable effects?</p> <p>Benefits outweigh harms Harms outweigh benefits Benefits = harms or Uncertain</p> <p><input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/></p>	
THERAPEUTIC INTERCHANGE	<p>Therapeutic alternatives available:</p> <p>Yes No</p> <p><input type="checkbox"/> <input checked="" type="checkbox"/></p> <p>List the members of the group.</p> <p>List specific exclusion from the group:</p>	<p>Rationale for therapeutic alternatives included:</p> <p>References:</p> <p>Rationale for exclusion from the group:</p> <p>References:</p>
VALUES & PREFERENCES / ACCEPTABILITY	<p>Is there important uncertainty or variability about how much people value the options?</p> <p>Minor Major Uncertain</p> <p><input type="checkbox"/> <input type="checkbox"/> <input checked="" type="checkbox"/></p> <p>Is the option acceptable to key stakeholders?</p> <p>Yes No Uncertain</p> <p><input type="checkbox"/> <input type="checkbox"/> <input checked="" type="checkbox"/></p>	

RESOURCE USE	<p>How large are the resource requirements?</p> <p>More intensive <input type="checkbox"/> Less intensive <input type="checkbox"/> Uncertain <input type="checkbox"/></p>	<p>Cost of medicines/ month:</p> <table border="1"> <thead> <tr> <th>Medicine</th> <th>Cost (ZAR)</th> </tr> </thead> <tbody> <tr> <td colspan="2">14 Day course</td> </tr> <tr> <td>Amoxicillin 1g 8hrly x 14 days*</td> <td>R 39.31</td> </tr> <tr> <td>Probenecid 750 mg daily**</td> <td>R 76.25</td> </tr> <tr> <td>Total cost/course</td> <td>R 115.57</td> </tr> <tr> <td colspan="2">28 Day course (Late syphilis)</td> </tr> <tr> <td>Amoxicillin 1g 8hrly x 28 days*</td> <td>R 78.63</td> </tr> <tr> <td>Probenecid 750 mg daily**</td> <td>R 152.51</td> </tr> <tr> <td>Total cost/course</td> <td>R 231.14</td> </tr> <tr> <td colspan="2">Other antibiotic options</td> </tr> <tr> <td>Doxycycline 100m daily x 14 days**</td> <td>R 8.45</td> </tr> <tr> <td>Doxycycline 100m daily x 28 days**</td> <td>R 16.04</td> </tr> <tr> <td>Benzathine benzylpenicillin, IM, 2.4 MU single dose***</td> <td>R 11.70</td> </tr> <tr> <td>Benzathine benzylpenicillin, IM, 2.4 MU once weekly x 3 weeks ***</td> <td>R 35.10</td> </tr> </tbody> </table> <p>*Contract circular RT301-2017 **SEP database, 4 December 2017 ***Equity quotation – S21 authorisation</p> <p>Additional resources: n/a</p>	Medicine	Cost (ZAR)	14 Day course		Amoxicillin 1g 8hrly x 14 days*	R 39.31	Probenecid 750 mg daily**	R 76.25	Total cost/course	R 115.57	28 Day course (Late syphilis)		Amoxicillin 1g 8hrly x 28 days*	R 78.63	Probenecid 750 mg daily**	R 152.51	Total cost/course	R 231.14	Other antibiotic options		Doxycycline 100m daily x 14 days**	R 8.45	Doxycycline 100m daily x 28 days**	R 16.04	Benzathine benzylpenicillin, IM, 2.4 MU single dose***	R 11.70	Benzathine benzylpenicillin, IM, 2.4 MU once weekly x 3 weeks ***	R 35.10
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EQUITY	<p>Would there be an impact on health inequity?</p> <p>Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> Uncertain <input type="checkbox"/></p>																													
FEASIBILITY	<p>Is the implementation of this recommendation feasible?</p> <p>Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Uncertain <input type="checkbox"/></p>																													

Type of recommendation	We recommend against the option and for the alternative	We suggest not to use the option or to use the alternative	We suggest using either the option or the alternative	We suggest using the option	We recommend the option
	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>

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 for all patients treated with this regimen, as tolerability in pregnancy and adherence may be problematic and little 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 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 Study

Review indicator:

Evidence of efficacy	Evidence of harm	Price reduction
<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

VEN status:

Vital	Essential	Necessary
<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Monitoring and evaluation considerations

Research priorities

References:

1. 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.
2. Katanami Y, Hashimoto T, Takaya S, Yamamoto K, Kutsuna S, Takeshita N, et al. Amoxicillin and Ceftriaxone as Treatment Alternatives to Penicillin for Maternal Syphilis. Emerging infectious diseases. 2017;23(5):827-9.
3. Morrison RE, Harrison SM, Tramont EC. Oral amoxycillin, an alternative treatment for neurosyphilis. Genitourin Med. 1985;61(6):359-62.
4. Faber WR, Bos JD, Rietra PJ, Fass H, Van Eijk RV. Treponemicidal levels of amoxicillin in cerebrospinal fluid after oral administration. Sex Transm Dis. 1983;10(3):148-50.