South African National Essential Medicine List
Primary Health Care Medication Review Process
Component: Ear, nose and throat conditions

MEDICINE REVIEW:

1. **Executive Summary**

Date:13 October 2016
Medicine (INN): Amoxicillin
Medicine (ATC): J01CA
Indication (ICD10 codes): J03.0/J03.8-9/J35.0/J02.0/J02.8-9/J31.1-2
Patient population: Adults and paediatrics
Level of Care: Primary level of care
Prescriber Level: Nurse practitioner
Current standard of Care: Phenoxymethylpenicillin
Efficacy estimates: Non-inferiority study with pre-specified non-inferiority margin of ≤10% for the upper limit (UL) of the 95% confidence interval (CI) of between-treatment difference in the incidence of positive cultures. ULs 95% CIs for differences between amoxicillin and penicillin were 4.9% at visit 2 (days 3–6); 6.5% at visit 3 (days 12-16); and 8.5% at visit 4 (days 26-36).
Motivator/reviewer name(s): Ms Shanene Olivier and Ms Pearl Lentsoane
PTC affiliation: n/a

2. **Name of author(s)/motivator(s):** Ms Shanene Oliviera[1] and Ms Pearl Lentsoane[2]

3. **Author affiliation and conflict of interest details:**
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4. **Introduction/ Background**
   At present, phenoxymethylpenicillin is the first line oral antibiotic for the treatment of tonsillitis and pharyngitis. Currently the Department of Health is experiencing a supply challenge and phenoxymethylpenicillin is being purchased as a Section 21 drug. An alternative option needs to be explored.

5. **Purpose/Objective i.e. PICO question**
   -P: Adults and paediatric patients
   -I: Amoxicillin, oral
   -C: Phenoxymethylpenicillin, oral
   -O: Cure of acute tonsillitis/pharyngitis Streptococcal tonsillitis and pharyngitis

6. **Methods:**
   a. **Data sources: PubMed**
   b. **Search strategy**
   " Amoxicillin as treatment for acute Streptococcal tonsillitis and pharyngitis".
   c. **Excluded studies:**

***Author**, date*	*Type of study*	*Reason for exclusion*
Gooch,W.(1993)(1)	Randomized evaluator-blinded	Comparison made between Pen V and Cefuroxime.

d. Evidence synthesis

Author, date	*Type of study*	n	Population	Comparators	Primary outcome	Effect sizes	Comments
Gerber, M. 2009(2)	AHA Scientific Statement updated from 1995.	Multiple RCT's, meta-analysis, single randomized trials and nonrandomized studies. **Studies done since 1995 to date.**	AHA recommendation for developing countries	Oral Penicillin's, Intramuscular Benzathine Pen G and macrolides.	The oral antibiotics of choice are penicillin V and amoxicillin	Class I, B	Once daily amoxicillin for 10 days has been shown to be effective for GAS pharyngitis due to the advantage of a broad spectrum agent. It is inexpensive and more palatable than Pen V. IM Pen G should be considered for patients unlikely to complete a 10 day course or oral therapy with a family history of rheumatic fever, rheumatic heart disease or environmental factors e.g. crowded living conditions, low socio-economic status.
Lennon et al. 2008(3)	Randomized non-inferiority trial	n=353 (n=177 randomized to amoxicillin , n=176 to pen V, for a period of 10 days in both groups)	353 Children with +ve throat swabs for GABHS	Amoxicillin and PenV oral antibiotics	Eradication of GABHS at visits 2, 3, and 4. The prespecified non-inferiority margin was the upper limit of the 95% confidence interval for the difference	At visit 2 (days 3–6): between treatment difference in the incidence of positive cultures was0.3% (UL 95% CI 4.9%); with a bacteriological failure of5.8% for amoxicillin vs. 6.2% for penicillin. At visit 3 (days 12–16): bacteriological failure was 12.7% vs 11.9% (UL 95% CI for difference 6.5%).At visit 4 (days 26–36): between treatment difference of 1.9% (UL 95% CI 8.5%); with	Amoxicillin, oral, daily is not inferior to twice daily penicillin V for the eradication of GABHS.

					between treatments of≤10%.	bacteriological failure of 10.7% vs 11.3%.	
Clegg et al (2006)(4)	Randomized, controlled, investigator-blinded, non-inferior trial.	n= 652 (n=326 randomized to amoxicillin once daily dosing, n=326 to amoxicillin twice daily dosing for a period of 10 days in both groups),)	Children 3-18 years old who had symptoms suggestive of Group A streptococcal (GAS) pharyngitis.	Stratified by weight (<40kg or ≥40kg) and then randomly assigned to receive once-daily (750mg or 1000mg) or twice daily (2 doses of 375mg or 500mg) Amoxicillin for 10 days.	Primary outcome: bacteriological failure at visit 2. The pre-specified non-inferiority margin was 10%.	At visit 2(14-21 days), failure rates were 20.1% (59/294) for the once-daily group vs 15.5% (46 /296) for the twice-daily group (difference, 4.53%; 90% CI -0.6 to 9.7). At visit 3(28-35 days), failure rates were 2.8% (6/216) vs 7.1% (16/225);difference, -4.33; 90% CI, -7.7 to -1.0).Frequency of git and other adverse events comparable in the treatment groups. Presumed allergic reactions-0.9% (6/ 635). Compliance reported to be > 95% (516/ 541) with 10 days of therapy with no significant differences between groups.	The study found that treatment for GAS pharyngitis, amoxicillin given once daily is not inferior to twice daily amoxicillin. The study concludes that once daily amoxicillin is suitable, especially in circumstances when daily dosing would improve adherence.

Guidelines

- **Brink et al:**

These guidelines are an update of the previous upper respiratory tract infections guidelines in South Africa published in 2004 and 2008in the SAMJ and South African Journal of Epidemiology and Infection, respectively. A group of multidisciplinary experts were invited to prepare the current recommendation alongside the Infectious Disease Society of Southern Africa.

This was urged by a worldwide increase in antibiotic resistance, and studies suggested that this is contributed to by inappropriate use of antibiotics, particularly for URTIs.

In the guidelines the following recommendations for the management of upper respiratory tract infections in South Africa covering acute pharyngotonsillitis caused by Group A β - Hemolytic Streptococci (GABS) were made:

- Amoxicillin as an alternative to Pen VK with the added advantage of no food restrictions and that the rash that occurs when pharyngotonsilitis is caused by Epstein – Barr Virus (EBV) EBV infection is less common with amoxicillin than with ampicillin). Several trials have demonstrated non-inferiority of once daily amoxicillin to twice daily amoxicillin or PenVK. Once daily regimens may improve patient adherence(5).
- Amoxicillin dosing recommendation for acute pharyngotonsillitis:
    - **Children**: Amoxicillin 50mk/kg/d once daily (maximum 1000mg) for 10 days.
    - **Adolescents and Adults**: Amoxicillin 500-1 000mg twice daily (alternatively, 50mg/kg/d once daily (maximum 3 000mg) for 10 days.
    - Azithromycin and clarithromycin recommendation for β-lactam allergies.

- **Chiappini et al:-**

Review of 12 national guidelines; 6 European countries, 5 USA and 1 Canadian. Comparisons of the different guideline recommendations for the diagnosis and treatment of group A β – hemolytic streptococci pharyngitis among children and adults. Accurate recognition and prompt antibiotic treatment for streptococcal pharyngitis are recommended by all guideline authors. Although Pen V is the drug of choice, amoxicillin is reported to be equally effective and has high palatability, which makes it a suitable option for children(6).

Recommendation:

Amoxicillin, oral be recommended as an alternative to phenoxmethypenicillin, oral for the acute treatment of Streptococcal tonsillitis and pharyngitis in adults and children.

Rationale: Non-inferiority RCTs suggest that amoxicillin is comparable to phenoxymethylpenicillin in paediatrics; whilst Guidelines recommends oral amoxicillin in adults.

Level of Evidence: I RCTs (Paediatrics), III Guidelines (Adults).

EVIDENCE TO DECISION FRAMEWORK

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

<table>
<tr><td>RESOURCE USE</td><td>How large are the resource requirements?

More intensive ☐ Less intensive ☒ Uncertain ☐</td><td>Cost of medicines/ treatment course for an adult:
<table><tr><th>Medicine</th><th>Cost (ZAR)*</th></tr><tr><td>Phenoxymethylpenicillin , oral 500 mg, 12 hourly x 10 days</td><td>40 tab x 0.57= 22.80</td></tr><tr><td>Amoxicillin, oral, 1000 mg 12 hourly x 10 days</td><td>40 cap x 0.57 = 22.80</td></tr></table>CONTRACT CIRCULAR HP09-2015AI
Weighted average prices:
- Phenoxymethylpenicillin, 250 mg tab = ZAR 0.57
- Amoxicillin, 500 mg cap = ZAR 0.57</td></tr>
<tr><td>EQUITY</td><td>Would there be an impact on health inequity?

Yes ☐ No ☒ Uncertain ☐</td><td></td></tr>
<tr><td>FEASIBILITY</td><td>Is the implementation of this recommendation feasible?
Yes ☒ No ☐ Uncertain ☐</td><td></td></tr>
</table>

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
	☐	☐	☐	☒	☐

Recommendation

Amoxicillin, oral be reccommended.

Review indicator:

Evidence of efficacy ☒ Evidence of harm ☐ Price reduction ☐

VEN status:

Vital ☐ Essential ☒ Necessary ☐

Monitoring and evaluation considerations

Research priorities

References:

1. Gooch WM, McLinn SE, Aronovitz GH, Pichichero ME, Kumar A, Kaplan EL, et al. Efficacy of cefuroxime axetil suspension compared with that of penicillin V suspension in children with group A streptococcal pharyngitis. Antimicrob Agents Chemother. 1993;37(2):159–63.
2. Gerber MA, Baltimore RS, Eaton CB, Gewitz M, Rowley AH, Shulman ST, et al. Prevention of Rheumatic Fever and Diagnosis and Treatment of Acute Streptococcal Pharyngitis: A Scientific Statement From the American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee of the Council on Cardiovascular Disease. Circulation [Internet]. 2009;119(11):1541–51. Available from: http://circ.ahajournals.org/content/119/11/1541.abstract
3. Lennon DR, Farrell E, Martin DR, Stewart JM. Once-daily amoxicillin versus twice-daily penicillin V in group A beta-haemolytic streptococcal pharyngitis. Arch Dis Child. 2008;93(6):474–8.
4. Clegg HW, Ryan AG, Dallas SD, Kaplan EL, Johnson DR, Norton HJ, et al. Treatment of Streptococcal Pharyngitis With Once-Daily Compared With Twice-Daily Amoxicillin. Pediatr Infect Dis J [Internet]. 2006;25(9):761–7. Available from: http://content.wkhealth.com/linkback/openurl?sid=WKPTLP:landingpage&an=00006454-200609000-00002
5. Brink AJ, Cotton MF, Feldman C, Finlayson H, Friedman RL, Green R, et al. Updated recommendations for the management of upper respiratory tract infections in South Africa. South African Med J. 2015;105(5):345–52.
6. Chiappini E, Regoli M, Bonsignori F, Sollai S, Parretti A, Galli L, et al. Analysis of Different Recommendations From International Guidelines for the Management of Acute Pharyngitis in Adults and Children. Clin Ther [Internet]. Elsevier Inc.; 2011;33(1):48–58. Available from: http://dx.doi.org/10.1016/j.clinthera.2011.02.001