



health

Department:
Health
REPUBLIC OF SOUTH AFRICA



South African National Essential Medicine List PHC Medication Review Process Component: Infections and related conditions

MEDICINE REVIEW:

1. Executive Summary

Date: 6 February 2017

Medicine (INN): Azithromycin

Medicine (ATC): J01FA10

Indication (ICD10 code): Tick bite fever (condition recommended to be added to PHC EML) A68.1

Patient population: Children weighing <45kg with mild to moderate infection

Prevalence of condition: African tick-bite fever (TBF) is highly prevalent in Africa, with a sero-prevalence of 30-56% (1). Data show that over the past 35 years there were almost 200 confirmed cases of African TBF amongst international travelers, with the majority (~80%) of these occurring in travelers from South Africa (2). The condition is well reported amongst international travelers, while data on local populations are limited, due to lack of diagnosis in these areas(3). Annual case incidence rates of African TBF have been estimated as 60 - 80 cases per 10 000 patients in Zimbabwe(3). The incidence rate of infection has been estimated to be in the region of 4- 5% in visitors from Europe, which is higher than those for other febrile illnesses such as malaria and typhoid fever (4, 5).

Level of Care: Primary level of Care

Prescriber Level: Nurse Practitioner

Current standard of Care: Doxycycline is the standard of care for tick bite fever, but there is not a suitable formulation available at PHC level for children <45 kg.

Efficacy estimates: (preferably NNT): No evidence available for azithromycin in TBF. Time to fever resolution is similar to doxycycline in Mediterranean Spotted Fever (MSF).

Motivator/reviewer name(s): Dr TN Gengiah (Reviewer)

PTC affiliation: N/A

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

Author: Tanuja Gengiah*

3. Author affiliation and conflict of interest details

*Head of Pharmacy, Centre for the AIDS Programme of Research, University of KwaZulu-Natal

*Member: PHC expert review committee (2016).

4. Introduction/ Background

Doxycycline is the preferred agent for the treatment of tick bite fever in non-pregnant adults and children. The use of doxycycline for spotted fever group infections is supported by extensive clinical experience, and small clinical trials that have reported more rapid resolution of symptoms in those who received doxycycline compared with other agents. The recommended dose in children weighing 45kg and more is 100mg twice daily and for those weighing less than 45kg is 2.2mg/kg twice per day. The doxycycline formulations are currently available as 100mg capsules only, so azithromycin or clarithromycin may be a suitable alternative to treat mild infection at a PHC level. In severe infection, children will be referred for doxycycline or IV clarithromycin or IV chloramphenicol. The alternative to finding a suitable substitute for doxycycline at PHC level, with mild to moderate infection, would be to refer all paediatric patients for further care regardless of the severity of illness.

5. Purpose/Objective i.e. PICO question

- P(patient/population): Children who weigh less than 45kg with mild to moderate TBF infection
- I(intervention): Macrolide, oral
- C(comparator): Doxycycline, oral
- O(outcome): Cure of TBF and symptom resolution

6. Methods:

a. **Data sources:** Pubmed, UpToDate, MMWR, Cochrane library

b. Search strategy

- i. Cochrane library: Mesh term "Tick bite fever" resulted in retrieval of 5 hits. All were excluded. Four were for TBF prophylaxis, one was focused on Lyme arthritis and all were in adults.
- ii. Pubmed: Key words: "tick bite fever treatment AND paediatrics"; "Tick bite fever, doxycycline, spotted fever group infections, azithromycin, macrolides, clarithromycin, children".

Six articles were identified, two articles were included for the primary comparison, one article was included for therapeutic class comparison, one article was excluded for lack of macrolide comparator, one article was excluded as older macrolide comparisons and one article was excluded for lack of doxycycline comparator.

c. Excluded studies:

Author, date	Type of study	Reason for exclusion
Kumar, M 2011(6)	Prospective observational study in children <12 years	Patients were treated with a 10-day course of oral doxycycline (5 mg/kg/day BD) – no macrolide comparator
Colomba, C 2006 (7)	Case series, n=415 Median age was 6 years (range: 1 month-15 years)	No doxycycline comparator (azithromycin, clarithromycin and chloramphenicol were compared)
Munoz-Espin, T 1986 (8).	RCT, n=81, children 1-13 years	Older macrolide erythromycin stearate compared to . tetracycline hydrochloride

d. Evidence synthesis for primary comparison

Author, date	Type of study	n	Population	Comparators	Primary outcome	Effect sizes	Comments
Meloni et al, 1996 (9)	RCT	30	Children with *MSF (2-11 years)	Azithromycin (n=15), 3 days (10 mg/kg once a day) vs. Doxycycline (n=15), 5 days (5 mg/kg once a day)	Difference in time to defervescence between groups by comparing peak daily temperatures in both groups Improvement in clinical signs and symptoms	No statistical significant difference was observed regarding the mean of the peak daily temperature or resolution of clinical symptoms between the 2 groups (Stats not reported)	Both drugs were equally well tolerated and comparably effective. None of the patients presented with symptoms attributable to either treatment. <i>Study weakness:</i> Small sample sizes Open-label Objectives measures and comparisons not reported in statistical terms
Phimda et al, 2007 (10)	Multi-center open label RCT	296	Adults >14 years with suspected leptospirosis	Oral doxycycline 200mg in the first dose, followed by 100 mg every 12 h for 7 days	Primary outcome: Cure regarded as resolution of fever within 5 days after antibiotic start.	In patients with leptospirosis, the median time to fever clearance was 45h (range, 8-118h) in the doxycycline group and	Article added for biological plausibility due to paucity of data with direct comparisons between

Author, date	Type of study	n	Population	Comparators	Primary outcome	Effect sizes	Comments
			or scrub typhus—	(n=145) or a 3-day course of azithromycin (1 g initially, followed by 500 mg once daily for 2 days(n=151)).	Secondary outcome: Time to defervescence regarded as the time between first dose of study drug and time to oral temp <37.5°C, maintained for 2 consecutive measurements without antipyretics.	40h (range, 8-136h) in the azithromycin group, respectively (p= 0.45). In patients with scrub typhus, treatment failure occurred in 1 patient In the azithromycin group, the median time to fever clearance 48 h (range, 16 - 120 h) in the doxycycline group and 60 h (range, 12- 128 h) in the azithromycin group, respectively (P =0.13).	doxycycline and azithromycin in paediatric patients. Doxycycline and azithromycin were found to be highly effective against both leptospirosis and scrub typhus with comparable fever clearance with both treatments. However, adverse events occurred more frequently in the doxycycline group than in the azithromycin group 27.6% and 10.6%, respectively;(p =0.02). Study weakness Different organism from TBF Open label

*MSF: Mediterranean spotted fever

Evidence synthesis for therapeutic class substitution with the newer macrolides

Author, date	Type of study	n	Population	Comparators	Primary outcome	Effect sizes	Comments
Cascio et al, 2002(11)	Open label RCT	87	Children with *MSF <14 years average age, 5 years	Clarithromycin (15/mg/kg/day in 2 divided doses for 7 days) vs. azithromycin (10 mg/kg daily for 3 days)	Time to defervescence (axillary body temp of ≤ 37°C for at least 3 consecutive days. Body temperature was measured every 6 hours by nursing personnel not involved in the study.	Clarithromycin group (n=45): mean (+-SD) of 46.2h (+-36.4 h) (median, 32 h; range, 6–168 h) Azithromycin group (n=42): mean ((+SD) of 39.3(+31.3 h median, 28 h; range, 6–144 h). Time to achieve defervescence was longer in the clarithromycin group than the azithromycin group but the difference in time was not statistically significant (p=0.34)	Both drugs were equally well tolerated. Azithromycin offers the advantages of administration in a single daily dose and a shorter duration of therapy, which could increase compliance in children. <i>Study Weakness:</i> Study was not double blinded Small sample size

*MSF: Mediterranean spotted fever

e. Evidence quality:

There is limited evidence for the effective use of newer macrolides such as azithromycin for treatment of paediatric MSF where the implicated organism is *R. Conorii*. This evidence is presented under the assumption that the newer macrolides are as effective in other spotted fever group infections such as *R. Africae* which is implicated in African Tick Bite Fever.

7. Alternative agents:

Clarithromycin 7.5mg/kg, oral, 12 hourly for 7 days is an alternative to azithromycin.

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 checked="" type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/></p>	
BENEFITS & HARMES	<p>Do the desirable effects outweigh the undesirable effects?</p> <p>Benefits outweigh harms Harms outweigh benefits Benefits = harms or Uncertain</p> <p><input checked="" type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/></p>	
THERAPEUTIC INTERCHANGE	<p>Therapeutic alternatives available:</p> <p>Yes No</p> <p><input checked="" type="checkbox"/> <input type="checkbox"/></p> <p>List the members of the group.</p> <p>List specific exclusion from the group:</p>	<p><u>Rationale for therapeutic alternatives included:</u></p> <ul style="list-style-type: none"> • Clarithromycin 7.5mg/kg, oral, 12 hourly, is as effective as azithromycin 10mg/kg, oral, daily for 3 days. <p><u>References:</u> Cascio A, Colomba C, Antinori S, Paterson DL, Titone L. Clarithromycin versus azithromycin in the treatment of Mediterranean spotted fever in children: a randomized controlled trial. Clin Infect Dis. 2002;34(2):154</p> <p>Rationale for exclusion from the group: n/a</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 checked="" type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/></p> <p>Is the option acceptable to key stakeholders?</p> <p>Yes No Uncertain</p> <p><input checked="" type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/></p>	

RESOURCE USE	How large are the resource requirements? More intensive <input type="checkbox"/> Less intensive <input checked="" type="checkbox"/> Uncertain <input type="checkbox"/>	Cost of medicines/course for 30kg child: <table border="1"> <thead> <tr> <th>Medicine</th> <th>Cost (ZAR)*</th> </tr> </thead> <tbody> <tr> <td>Azithromycin, oral, 250 mg/day x 3 days</td> <td>R 8.84</td> </tr> <tr> <td>Clarithromycin, oral, 450 mg/day x 7 days</td> <td>R 55.39</td> </tr> </tbody> </table>	Medicine	Cost (ZAR)*	Azithromycin, oral, 250 mg/day x 3 days	R 8.84	Clarithromycin, oral, 450 mg/day x 7 days	R 55.39
	Medicine	Cost (ZAR)*						
Azithromycin, oral, 250 mg/day x 3 days	R 8.84							
Clarithromycin, oral, 450 mg/day x 7 days	R 55.39							
		*Contract circular HP02-2015AI Additional resources: n/a						
EQUITY	Would there be an impact on health inequity? Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> Uncertain <input type="checkbox"/>							
FEASIBILITY	Is the implementation of this recommendation feasible? Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Uncertain <input type="checkbox"/>							

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

Review indicator:

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

VEN status:

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

Recommendation

Azithromycin 10mg/kg, oral, daily, for 3 days in children <45 kg with mild to moderate TBF.

Rationale: The current 100mg formulation of doxycycline precludes its administration to children <45kg. Although evidence is limited, azithromycin is effective against spotted fever group infections and can be safely dosed in paediatric patients with mild to moderate tick bite fever. Patients with severe tick bite fever, or those not responding to azithromycin, will be referred to a higher level of care.

Level of Evidence: II Disease-oriented RCT

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 type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>

Research priorities

Monitoring and evaluation considerations

References:

1. Dupont HT, Brouqui P, Faugere B, Raoult D. Prevalence of antibodies to *Coxiella burnetii*, *Rickettsia conorii*, and *Rickettsia typhi* in seven African countries. *Clin Infect Dis*. 1995;21(5):1126-33.
2. Jensenius M, Fournier PE, Hellum KB, Wesslen L, Caruso G, Prio T, et al. Sequential changes in hematologic and biochemical parameters in African tick bite fever. *Clin Microbiol Infect*. 2003;9(7):678-83.
3. Kelly PJ, Mason PR, Matthewman LA, Raoult D. Seroepidemiology of spotted fever group rickettsial infections in humans in Zimbabwe. *J Trop Med Hyg*. 1991;94(5):304-9.
4. Frean J, Blumberg L. Tick bite fever and Q fever - a South African perspective. *S Afr Med J*. 2007;97(11 Pt 3):1198-202.
5. Chapman AS, et al. Diagnosis and Management of Tickborne Rickettsial Diseases: Rocky Mountain Spotted Fever, Ehrlichioses, and Anaplasmosis ---United States. March 31, 2006 / 55(RR04);1-27, . *MMWR*. 2006.
6. Kumar M, Krishnamurthy S, Delhikumar CG, Narayanan P, Biswal N, Srinivasan S. Scrub typhus in children at a tertiary hospital in southern India: clinical profile and complications. *J Infect Public Health*. 2012;5(1):82-8.
7. Colomba C, Saporito L, Polara VF, Rubino R, Titone L. Mediterranean spotted fever: clinical and laboratory characteristics of 415 Sicilian children. *BMC Infect Dis*. 2006;6:60.
8. Munoz-Espin T, Lopez-Pares P, Espejo-Arenas E, Font-Creus B, Martinez-Vila I, Traveria-Casanova J, et al. Erythromycin versus tetracycline for treatment of Mediterranean spotted fever. *Arch Dis Child*. 1986;61(10):1027-9.
9. Meloni G, Meloni T. Azithromycin vs. doxycycline for Mediterranean spotted fever. *Pediatr Infect Dis J*. 1996;15(11):1042-4.
10. Phimda K, Hoontrakul S, Suttinont C, Chareonwat S, Losuwanaluk K, Chueasuwanchai S, et al. Doxycycline versus azithromycin for treatment of leptospirosis and scrub typhus. *Antimicrob Agents Chemother*. 2007;51(9):3259-63.
11. Cascio A, Colomba C, Antinori S, Paterson DL, Titone L. Clarithromycin versus azithromycin in the treatment of Mediterranean spotted fever in children: a randomized controlled trial. *Clin Infect Dis*. 2002;34(2):154-8.