Antibiotic prevention and management of laboratory confirmed Strep A skin infections to prevent acute rheumatic fever and rheumatic heart disease: A systematic review

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Antibiotic prevention and management of laboratory-confirmed Strep A skin infections to prevent acute rheumatic fever and rheumatic heart disease: *A systematic review*

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1 Introduction

Rheumatic heart disease (RHD) and acute rheumatic fever (ARF), sequelae of untreated group A β-haemolytic streptococcus (Strep A) infection, remain a public health concern in low and middle-income countries (LMIC) [1]. Laboratory confirmation of causative pathogens of SSSIs can direct antimicrobial therapy, specifically clearance of Strep A. While there are several national guidelines for managing Strep A infection, specifically pharyngitis and tonsilitis there are, however, no definitive global treatment guidelines exist for Strep A skin infections.

2 Aim

This systematic review sought to synthesize evidence, from published and unpublished studies, on the effectiveness of routinely-used directed antibiotic therapy, compared to no treatment or an alternative antibiotic to treat Strep A skin infections, in preventing ARF and RHD

3 Method

We searched PubMed, Scopus, Cochrane Library, and clinical trial registries for published trials and ongoing or completed relevant trials (Dec 2022). Conference proceedings of relevant meetings of the last three years were scanned for unpublished trials. The effectiveness of antibiotic therapy was measured by assessing the eradication rate of Strep A and the clinical resolution of uncomplicated polymicrobial skin infections (that included mild to severe impetigo, cellulitis, abscess, infected ulcers, wound infection, furuncules, perianal dermatitis, skin ulcers, infected eczema). We assessed quality of included RCTs using the ROB 2 tool focusing on primary outcomes. We present meta-analyses reporting Risk Ratio (RR) with 95% CI where possible. The certainty of the evidence was ascertained using GRADE methodology. Screening, data extraction was performed in duplicate with a third reviewer arbitrating where necessary.

4 Results

Table 1. Included studies (n=12)

Author, year	Region, setting	Population (n); range of age	SSSI	Study drugs*	*At baseline*	
					Strep A	*S aureus*
• *Penicillin comparisons*						
Amaya-Tapia 1993	Mexico, NR	Adults (n=62); 17.5 to 62.1 years	Uncomplicated SSSIs	Azithromycin, oral *vs* Dicloxacillin, oral	4.9%	55.7%
Bowen 2014	Northern Territory of Australia (Aboriginal communities), primary care	Children (n=508); 4.6 to 8.8 years	Purulent/ crusted non-bullous impetigo	Cotrimoxazole, oral *vs* Benzathine Pen G, IM	89.6%	81.1% (Both: 74.2%)
Meury 2008	Switzerland, outpatients	Children (n=35); 1.1 to 11.6 years	Perianal dermatitis	Cefuroxime, oral** *Vs* Penicillin, oral	100%	NR
Rodriguez-Solans, 1993	Central & South America (Costa Rica, Guatemala, Panama, Venezuela), NR	Children (n=118); 1 to 12 years	Uncomplicated SSSIs	Azithromycin, oral *vs* Cloxacillin ester, oral (cloxacillin/flucloxacillin)	10.5%	80.2%
Tong, 2010	Northern Territory, Australia (Aboriginal children), primary care	Children (n=13); 2 months to 16 years	Purulent/crusted impetigo	Cotrimoxazole, oral *vs* Benzathine Pen G, IM	30.8%	100%
Villiger, 1987	New Zealand, primary care	Adults/ children (n=200); 1 to 78 years	Uncomplicated SSSIs	Mupirocin, topical *vs* Oral antibiotics (flucloxacillin/erythromycin)	2.1%	57.8%
• *Cephalosporin comparisons*						
Bass, 1997	Honolulu, Hawaii, primary care	Children (n=32); 3.25 to 4.35 years	Impetigo	Mupirocin/ Bacitracin, topical *vs* Cephalexin, oral*	0% (Both: 13.6%)	100%
Bucko, 2002	United States, primary care	Adults/ children (n=1685); 12 to 95 years	Uncomplicated SSSIs	Cefditoren, oral*** *vs* Cefadroxil*/Cefuroxime, oral**	4.2%	46.7%
Gooch, 1991	United States, outpatients	Adults/ children (n=330); 4 to 90 years	Uncomplicated SSSIs	Cefuroxime, oral** *vs* Cephalexin*/Cefadroxil, oral*	5.1%	41.4%
Jacobs, 1992	United States, NR	Children (n=238); 60.8 to 72.9 months	Uncomplicated SSSIs	Cefuroxime, oral** *vs* Cefadroxil, oral*	33.8%	66.2% (Both: 15.6%)
Neldner, 1991	United States, primary care, NR	Adults (n=374); 17 to 82 years	Uncomplicated SSSIs	Temafloxacin, oral *vs* Cefadroxil, oral*	4.0%	41.0%
Wible, 2003	United States, Canada, Mexico, Argentina, Brazil, Chile and Peru, outpatients	Children (n=499); 4.9 to 17.9 years	Uncomplicated SSSIs	Linezolid, oral *vs* Cefadroxil, oral*	13.2%	57.5%

Benzathine Pen G: Benzathine benzylpenicillin G; ***IM***: intramuscular; ***n***:sample size; ***NR***: not reported; *1st generation cephalosporin = cephalexin, cefadroxil; **2nd generation cephalosporin = cefuroxime; ***3rd generation cephalosporin = cefditoren

4 Results, cont'

Twelve RCTs (4 in LMICs, 7 in HICs and 1 LMIC/HIC settings) evaluating penicillin (6 studies) and cephalosporins (6 studies) against other antibiotics, were included in the evidence synthesis (Table 1). Clinically-suspected SSSIs were microbiologically-confirmed on culture as Strep A infections. No trial explicitly reported on the duration and severity of Strep A SSSIs, rheumatic fever or heart disease rates, or provider and patient acceptability of therapy for evidence synthesis.

Table 2. Evidence for antibiotics effectiveness for clinical resolution

N	Antibiotic 1	Antibiotic 2	Relative Effect	Certainty
503	Cotrimoxazole, oral	Penicillin, IM	RR 0.97 (0.90 to 1.05)	⊕⊕⊕◯ Moderate
179	Macrolide, oral	Penicillin, oral	RR 1.00 (0.95 to 1.06)	⊕⊕◯◯ Low
181	Mupirocin, topical	Penicillin, oral	RR 1.00 (0.97 to 1.03)	⊕◯◯◯ Very low
201	Fluroquiolone, oral	Cephalosporin, oral	RR 1.00 (0.94 to 1.05)	⊕◯◯◯ Very low
431	Linezolid, oral	Cephalosporin, oral	RR 1.01 (0.95 to 1.07)	⊕⊕◯◯ Low
19	Bacitracin, topical	Cephalosporin, oral	RR 0.37 (0.16 to 0.86)	⊕◯◯◯ Very low
17	Mupirocin, topical	Cephalosporin, oral	RR 1.00 (0.80 to 1.25)	⊕◯◯◯ Very low
578	2nd gen cephalosporin, oral	1st gen cephalosporin, oral	RR 1.18 (1.08 to 1.29)	⊕⊕◯◯ Low
1263	3rd gen cephalosporin, oral	1st/2nd gen cephalosporin, oral	RR 1.68 (1.53 to 1.84)	⊕⊕⊕◯ Moderate

The evidence is very uncertain about the effect of antibiotics on microbiological Strep A eradication rate. Adverse events included pain at the injection-site at 48 hours (IM benzathine benzylpenicillin), mild gastrointestinal adverse events (oral antibiotic therapies, cephalosporins (cefadroxil, cephalexin, cefuroxime, loracarbef, cefaclor, cefditoren), but was predominant with use of cefditoren (moderate certainty evidence). Serious treatment-associated adverse events included an injection site buttock abscess from which S aureus was cultured, associated with IM benzathine benzylpenicillin and elevated lipase level, in a study participant with comorbid viral gastroenteritis, associated with oral linezolid. Cotrimoxazole probably results in little to no difference in antibiotic resistance compared to IM benzathine benzylpenicillin, moderate certainty evidence – with all Strep A isolates susceptible to penicillin vs seven (1.54%) resistant to cotrimoxazole.

5 Conclusions

The few studies with several methodological limitations and uncertainty of the evidence warrant cautious interpretation. For the directed treatment of Strep A SSSIs to prevent ARF/RHD, more robust, high-quality studies are needed to determine the preferred choice of antibiotic. Resistance patterns, availability and cost are important local contextual factors to guide selection of antibiotics to treat Strep A SSSIs.

6 References

1. World Health Organization; 2023 [cited 2023 Oct 20]. Available from: https://www.who.int/news-room/fact-sheets/detail/rheumatic-heart-disease

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