

**South African National Essential Medicines List
Adult Hospital Level Medication Review Process
Component: Obstetrics**

MEDICINE REVIEW

1. Executive summary

Date: 21 November 2017
Medicine: Cefuroxime
ATC code: J01DC02 (Second generation cephalosporin)
Indication (ICD10 code): Urinary tract infection (UTI) during pregnancy (O23.1)
Patient population: Pregnant women with symptomatic UTI
Prevalence of the condition: Up to 10% of all pregnant women
Level of care: Primary health care/Hospital level
Prescriber level: Nurse/Doctor
Current standard of care: Nitrofurantoin
Efficacy estimates (preferably NNT): n/a
Motivator/reviewer name(s): Ebrahim Bera
PTC affiliation: PTC: Rahima Moosa Mother-and-Child Hospital

2. Name of authors/motivators: Ebrahim Bera

3. Author affiliation/ Conflict of interest: University of Witwatersrand, Adult Hospital Level Committee (2017-2020); no conflict of interests declared.

4. Introduction/Background

Urinary tract infections in pregnancy are common, occurring in up to 10% of all pregnancies, and may lead to pyelonephritis, preterm labour, preterm prelabour rupture of membranes (PPROM), and the sequelae of preterm birth.¹ Pathogens causing UTI also cause release of cytokines and prostaglandin production, which trigger cervical softening and stimulate oxytocin receptors. This in turn may lead to preterm labour. Additionally, severe disease may result in septic shock, renal dysfunction and maternal death. The diagnosis of UTI is usually clinical, with symptoms of dysuria, frequency of micturition and lower abdominal pain, usually without fever. Leucocytes and/or nitrates may be present on urine dipsticks. The commonest pathogens isolated are Gram-negative bacilli, of which E coli is most often cultured.²

5. Purpose/Objective i.e. PICO

Nitrofurantoin is currently recommended as the treatment of choice, but there have been reports of availability of supply concerns on several occasions.

To determine which antibiotic could be recommended in the event nitrofurantoin is not available.

P – pregnant women with UTI

I – cefuroxime

C – nitrofurantoin

O – cure rates, recurrence of UTI

6. Methods

Search strategy

A Pubmed literature search using the following terminology was performed: “cefuroxime” [Substance Name] OR “cefuroxime [Text Word] AND “urinary tract infection” [Text Word] OR “urinary tract infection” [MeSH Terms] AND (“1989/12/31” [PDAT] : “2017/06/01” [PDAT]) AND

“human” [MeSH Terms] AND English [lang]) AND (randomized controlled trial [Publication Type] OR (randomized [Title/Abstract] AND controlled [Title/Abstract] AND trial [Title/Abstract]))
 No head-to-head studies of nitrofurantoin compared with cefuroxime were identified.

Evidence synthesis

Author, date	Type of study	n	Population	Comparators	Primary outcome	Effect size	Comments
Estebanez et al 2009(3)	Randomised controlled trial	109	Pregnant women with UTI confirmed on urine culture	Fosfomycin(FF) 3g stat vs. amoxicillin / clavulanic acid (AC) 500/125mg 8 hourly for 7 days	Microbiological cure	Sterile culture ffg Rx: 80% AC vs 83% FF; RR 1.2 (95%CI 0.5 to 3.2). Recurrence RR 1.1 (95% CI 0.1 to 10.1).	Study was not double-blind. AC is non-inferior to FF for microbiol cure, but adherence better with FF. No data on pregnancy outcomes
Usta et al 2011 (4)	Randomised controlled trial	90	Pregnant women with UTI confirmed on urine culture	FF 3g stat vs. AC 625mg BD vs. cefuroxime (CEF) 500mg BD	Negative urine culture at week 2 post Rx	Sterile culture at week 2 was 82% FF; 82% AC; 90% CEF. No diff in AE or SAEs	Study was not double-blind. Microbiological cure rate similar. Better adherence with FF. No data on pregnancy outcomes
Vazquez et al 2011 (5)	Cochrane review	10 RCTs; n= 1125	Pregnant women with symptomatic UTI	Various antibiotic regimens	Cure rate Recurrent infection Neonatal outcomes	No difference in outcome. Cure rates very high.	Methodology robust. Few studies from LMICs.
Lewis et al 2013 (6)	Cross sectional analytical study. Antimicrobial susceptibility	425	Adults with confirmed UTI (pregnant women = 19)	Commonly used antibiotics for UTI	GNB, GPC susceptibility	FF 96%, CEF 90%, AC 83%, nitrofurantoin 92%.	Small study, in Gauteng, very few pregnant women

Evidence quality

The included studies are of moderate quality. A number of limitations – the studies were not double-blind, the participant numbers were small, the endpoints, although clinically relevant, did not include neonatal outcomes. Nonetheless, it appears that commonly used antibiotics – cefuroxime, fosfomycin & amoxicillin/clavulanic acid are very effective in eradicating pathogens causing UTI in pregnancy. Although no studies were found comparing nitrofurantoin with cefuroxime, the antimicrobial susceptibility data show high susceptibility of Gram negative bacilli (GNB) to fosfomycin (98%), cefuroxime (93%), and nitrofurantoin (91%). GNB susceptibility to amoxicillin/clavulanic acid is 81%.

The most suitable alternative to nitrofurantoin would be fosfomycin or cefuroxime.

7. Other considerations

The cost of fosfomycin in SA is R188.67 (SEP database, 27 May 2017) whereas in Turkey its R49.04, in Hungary R21.93, in Austria R57.09, and in Germany R73.76 (International prices sourced on 23 February 2016).

In South Africa fosfomycin may be more expensive than cefuroxime (SEP database 27 May 2017; 80 % of SEP: R150.94 and R88.92, respectively).

Adherence was unsurprisingly found to be superior with fosfomycin in all the studies, since it is a single dose.

8. Contra-indications

Fosfomycin and cefuroxime are both classified as FDA category B – no evidence of fetal harm when used in pregnancy.

9. Warnings

Amoxicillin/clavulanic acid has been associated with necrotising enterocolitis in preterm neonates, when prescribed for pregnant women with PPROM.⁷For this reason there has been a sharp reduction (unjustly) in its general prescribing by obstetricians.

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>	See above.								
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 checked="" type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/></p>	See above.								
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: Nitrofurantoin, Fosfomycin</p> <p>List specific exclusion from the group: n/a</p>	<p>Rationale for therapeutic alternatives included:</p> <p>Current standard of care in the</p> <p>References: Adult Hospital Level STGs and EML, 2015 edition</p> <p>Rationale for exclusion from the group: n/a</p> <p>References: n/a</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 checked="" type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/></p>									
RESOURCE USE	<p>How large are the resource requirements?</p> <p>More intensive Less intensive Uncertain</p> <p><input type="checkbox"/> <input type="checkbox"/> <input checked="" type="checkbox"/></p>	<p>Price of medicines/ treatment course:</p> <table border="1"> <thead> <tr> <th>Medicine</th> <th>Cost (ZAR)</th> </tr> </thead> <tbody> <tr> <td>Nitrofurantoin 100mg 6 hourly x 5d, (40 caps)</td> <td>199.21 *</td> </tr> <tr> <td>Fosfomycin 3g (1 sachet)</td> <td>103.26*</td> </tr> <tr> <td>Cefuroxime 250 mg 12 hourly x 5d, (10 tabs)</td> <td>111.04**</td> </tr> </tbody> </table> <p>* Contract circular HP02-2019AI: ** SEP (cheapest generic), accessed 24 November 2019. https://mpr.code4sa.org/ Additional resources: n/a</p>	Medicine	Cost (ZAR)	Nitrofurantoin 100mg 6 hourly x 5d, (40 caps)	199.21 *	Fosfomycin 3g (1 sachet)	103.26*	Cefuroxime 250 mg 12 hourly x 5d, (10 tabs)	111.04**
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EQUITY	<p>Would there be an impact on health inequity?</p> <p>Yes No Uncertain</p> <p><input type="checkbox"/> <input type="checkbox"/> <input checked="" type="checkbox"/></p>									

FEASIBILITY Y	Is the implementation of this recommendation feasible?			
	Yes <input type="checkbox"/>	No <input type="checkbox"/>	Uncertain <input checked="" type="checkbox"/>	

Type of recommendation	We recommend against the option and for the alternatives <input checked="" 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 type="checkbox"/>	We recommend the option <input type="checkbox"/>
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Recommendation: Based on the review of the evidence above, the Adult Hospital Level Committee proposed that cefuroxime be recommended in the event nitrofurantoin is not available. **However, at the NEMLC meeting of 1 February 2018 the NEMLC did not accept the Adult Hospital Level Committee recommendation to include cefuroxime on the Adult Hospital Level EML.**

Rationale: Despite cefuroxime being comparable to fosfomycin in terms of effectiveness and safety, fosfomycin is administered as a single dose. NEMLC noted that nitrofurantoin and fosfomycin are currently recommended for uncomplicated cystitis and considered this to be sufficient. Cefuroxime could be considered if nitrofurantoin is out of stock, but should be recommended via a circular. Furthermore, introducing second-generation cephalosporin, cefuroxime, to the EML for this indication would probably result in indication creep.

Level of Evidence: I Systematic review, Susceptibility data, Expert opinion

Review indicator: Current local susceptibility studies for community acquired uncomplicated UTI.

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

VEN status: n/a

M&E considerations

Research priorities: Current local susceptibility studies for community acquired uncomplicated UTI.

References

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2. Minardi D, d'Anzo G, Cantoro D, Conti A, Muzzonigro G. Urinary tract infections in women: etiology and treatment options. *Int J Gen Med* 2011; 4: 333-43.
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