**South African National Essential Medicine List**
**Adult Hospital Level Medication Review Process**
**Component: Kidney and urology disorders**

## EVIDENCE SUMMARY

**Date:** 29 October 2020
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### QUESTION: Alternatives to ciprofloxacin to treat community acquired uncomplicated cystitis

**Background:** NEMLC had recommended gentamicin, IM as a single dose (doctor prescribed) be considered as first line option for community acquired urinary tract infection (UTI) at primary level of care[1]. Subsequently, it was proposed that as nurse prescribers administer gentamicin, the option of fixed dosing or a maximum dose be considered and that the feasibility of administering large volumes of parenteral gentamicin be reviewed[2].

The PHC/Adult Hospital Level Committee (2020-2023) undertook the review, but first reviewed the various antimicrobial options, noting that 25-42% of uncomplicated acute cystitis cases in women will resolve spontaneously[3].

### GENTAMICIN, IM AS A SINGLE DOSE:

*Evidence review:*
Refer to the previous NEMLC-approved gentamicin medicine review, based on a systematic review by Goodlet et al[4] of RCTs investigating a range of aminoglycosides.

*Concerns:*
- Limited data for adults – in a 2019 systematic review, all identified studies in adults used aminoglycosides other than gentamicin, and all were published 30 years or more ago[4].
- Concerns about potentially suboptimal intramuscular injection technique in obese patients, leading to decreased efficacy[5] [6].
- The small but non-trivial potential for nephrotoxicity, especially since baseline renal function will not be known for the vast majority of patients[7].
- Patient acceptability is unknown, considering that IM administration of gentamicin would be painful.

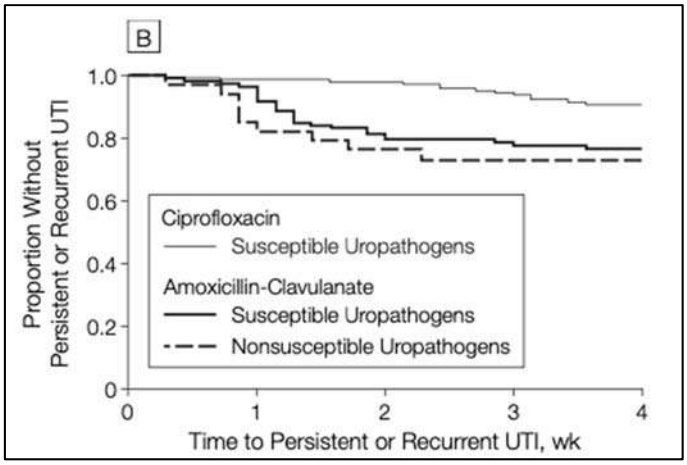
### AMOXICILLIN-CLAVULANATE VS CIPROFLOXACIN

*Evidence:* Single-blinded RCT[8] compared amoxicillin-clavulanate, oral (500/125 12 hourly for 3 days) vs ciprofloxacin, oral (250mg 12 hourly for 3 days) amongst 370 women with acute uncomplicated cystitis. The primary outcome was clinical cure (symptom-based) at 4 months and the secondary outcome, microbiological cure at 2 weeks and vaginal *E. coli* colonization at 2-week follow-up.

[1] Minutes of the NEMLC meeting of x17 September 2020
[2] Minutes of the NEMLC meeting of 30 September 2020
[3] Falagas ME, Kotsantis IK, Vouloumanou EK, Rafailidis PI. Antibiotics versus placebo in the treatment of women with uncomplicated cystitis: a meta-analysis of randomized controlled trials. J Infect. 2009 Feb;58(2):91-102. https://pubmed.ncbi.nlm.nih.gov/19195714/
[4] Goodlet KJ, Benhalima FZ, Nailor MD. A Systematic Review of Single-Dose Aminoglycoside Therapy for Urinary Tract Infection: Is It Time To Resurrect an Old Strategy? Antimicrob Agents Chemother. 2019;63(1).
[5] Palma S, Strohfus P. Are IM injections IM in obese and overweight females? A study in injection technique. Appl Nurs Res. 2013;26(4):e1-4. https://pubmed.ncbi.nlm.nih.gov/24156877/
[6] Nisbet AC. Intramuscular gluteal injections in the increasingly obese population: retrospective study. BMJ. 2006;332(7542):637-8. https://pubmed.ncbi.nlm.nih.gov/16524934/
[7] Hayward RS, Harding J, Molloy R, Land L, Longcroft-Neal K, Moore D, et al. Adverse effects of a single dose of gentamicin in adults: a systematic review. Br J Clin Pharmacol. 2018;84(2):223-38. https://pubmed.ncbi.nlm.nih.gov/28940715/
[8] Hooton TM, Scholes D, Gupta K, Stapleton AE, Roberts PL, Stamm WE. Amoxicillin-clavulanate vs ciprofloxacin for the treatment of uncomplicated cystitis in women: a randomized trial. JAMA. 2005 Feb 23;293(8):949-55. https://pubmed.ncbi.nlm.nih.gov/15728165/

*Results:*

- Lower clinical cure rate in amoxicillin-clavulanate group (58% vs 77%).
- Microbiological cure at 2 weeks in 95% of ciprofloxacin group vs 76% amoxicillin-clavulanate group.
- Higher rates of vaginal *E. coli* colonization at 2 weeks in 45% of amoxicillin-clavulanate group vs 10% in ciprofloxacin group.




**CEPHALOSPORINS**

*Evidence:* Double-blind RCT[9] of 300 women with acute uncomplicated cystitis comparing ciprofloxacin, oral (250 mg 12 hourly x 3 days) vs cefpodoxime, oral (100mg 12 hourly x 3 days).

*Results:*

- Overall clinical cure rate at the 30-day visit was 93% (139/150) for ciprofloxacin vs 82% (123/150) for cefpodoxime (difference of 11%; 95% CI, 3%-18%); ITT analysis and patients lost to follow-up were considered as responded to treatment.
- Criteria of non-inferiority (cefpodoxime would be non-inferior to ciprofloxacin by a 10% margin) was not met.

*Concerns:*

- Data is limited, and one RCT showed that cefpodoxime has poor cure rates (probably similar to cotrimoxazole – see table below).
- Extensive cephalosporin use may also result in collateral damage resulting in infections with extended-spectrum β-lactamase producing organisms (ESBLs).

**COTRIMOXAZOLE**

- Standard of care in many countries, and a 3-day course has been reported to be as effective as a 7-10 day course[10].
- Resistance has been reported to be a concern globally, but at least 50% of women infected with a resistant organism has been reported to be successfully treated with cotrimoxazole[11]. Clinical cure rates of 80-85% have been reported, even with resistance rates of ~30%.

*Concerns:*

- South African data (albeit limited data) suggests a low rate of cotrimoxazole susceptibility (see "Local Susceptibility Data" section below).

[9] Hooton TM, Roberts PL, Stapleton AE. Cefpodoxime vs ciprofloxacin for short-course treatment of acute uncomplicated cystitis: a randomized trial. JAMA. 2012 Feb 8;307(6):583-9. https://pubmed.ncbi.nlm.nih.gov/22318279/

[10] Warren JW, Abrutyn E, Hebel JR, Johnson JR, Schaeffer AJ, Stamm WE. Guidelines for antimicrobial treatment of uncomplicated acute bacterial cystitis and acute pyelonephritis in women. Infectious Diseases Society of America (IDSA). Clin Infect Dis. 1999 Oct;29(4):745-58. https://pubmed.ncbi.nlm.nih.gov/10589881/

[11] Gupta K, Hooton TM, Stamm WE. Increasing antimicrobial resistance and the management of uncomplicated community-acquired urinary tract infections. Ann Intern Med. 2001 Jul 3;135(1):41-50. https://pubmed.ncbi.nlm.nih.gov/11434731/

**NITROFURANTOIN**

- Adherence is a concern as only available in South Africa as a macrocrystalline formulation, taken 6 hourly for 5 days[12].
- Indicated for cystitis, not for pyelonephritis[12].
- Historically not recommended in patients with impaired GFR, but recent evidence[13] suggests that use in renal impairment is fine.
- Use of nitrofurantoin does not generate resistance to other classes of antimicrobials (no collateral damage).
- Generally a safe medicine, but may be associated with significant gastro-intestinal intolerance[12].

| Study (year) [reference] | | Treatment regimen | |
|---|---|---|---|
| **Iravani et al (1999) [37]** | **TMP-SMX, 160/800 mg twice daily for 7 days** | **Nitrofurantoin monohydrate/ macrocrystals, 100 mg twice daily for 7 days** | **Ciprofloxacin, 100 mg twice daily for 3 days** |
| Early clinical cure | 165/174 (95) | 166/179 (93) | 160/168 (95) |
| Early bacterial cure | 161/174 (93) | 153/177 (86) | 148/168 (88) |
| Late clinical cure | 137/153 (90) | 135/151 (89) | 132/147 (90) |
| Adverse events, % | 38 | 34 | 28 |
| **Arredondo-Garcia et al (2004) [35]** | **TMP-SMX, 160/800 mg twice daily x 7 days** | **Norfloxacin, 400 mgtwice daily for 7 days** | **Ciprofloxacin, 250 mg twice daily for 3 days** |
| Early clinical cure | 70/81 (86) | 90/107 (84) | 86/97 (89) |
| Early bacterial cure | 69/81 (85) | 93/107 (87) | 89/97 (92) |
| Late clinical cure | 66/81 (82) | 88/107 (82) | 81/97 (84) |
| Adverse events, % | 8.7 | 3.9 | 4.0 |
| **Kavatha et al (2003) [38]** | **TMP-SMX, 160/800 mgtwice daily for 3 days** | **Cefpodoxime proxetil, 100 mg twice daily for 3 days** | |
| Early clinical cure | 70/70 (100) | 62/63 (98.4) | |
| Early bacterial cure | 70/70 (100) | 62/63 (98.4) | |
| Late clinical cure | 51/60 (85) | 42/50 (84) | |
| Adverse events, % | 1.4 | 1.6 | |
| **Gupta et al (2007) [36]** | **TMP-SMX, 160/800 mgtwice daily for 3 days** | **Nitrofurantoin monohydrate/ macrocrystals, 100 mg twice daily for 5 days** | |
| Early clinical cure | 133/148 (90) | 144/160 (90) | |
| Early bacterial cure | 131/144 (91) | 141/154 (92) | |
| Late clinical cure | 117/148 (79) | 134/160 (84) | |
| Adverse events, % | 31 | 28% | |

**NOTE.** Data are proportion of subjects (%), unless otherwise indicated. Efficacy rates refer to cure rates on the visit closest to a 5–9-day period following treatment. NA, not available; TMP-SMX, trimethoprim-sulfamethoxazole.

*Studies: Iravani A et al. A trial comparing low-dose, short-course ciprofloxacin and standard 7 day therapy with co-trimoxazole or nitrofurantoin in the treatment of uncomplicated urinary tract infection. J Antimicrob Chemother. 1999 Mar;43 Suppl A:67-75; Arredondo-Garcia JL et al. Comparison of short-term treatment regimen of ciprofloxacin versus long-term treatment regimens of trimethoprim/sulfamethoxazole or norfloxacin for uncomplicated lower urinary tract infections: a randomized, multicentre, open-label, prospective study. J Antimicrob Chemother. 2004;54:840-843; Kavatha D et al. Cefpodoxime-proxetil versus trimethoprim-sulfamethoxazole for short-term therapy of uncomplicated acute cystitis in women. Antimicrob Agents Chemother. 2003;47:897-900; Gupta K et al. Short-course nitrofurantoin for the treatment of acute uncomplicated cystitis in women. Arch Intern Med. 2007;167:2207-2212.*

**Fosfomycin**

*Evidence:*

*Falagas et al (2010):* Meta-analysis of 27 RCTs showed no difference in microbiological or clinical cure rates between fosfomycin and other agents (quinolones, nitrofurantoin, etc.)

[12] SAMF, 2016

[13] Santos JM, Batech M, Pelter MA, Deamer RL. Evaluation of the Risk of Nitrofurantoin Lung Injury and Its Efficacy in Diminished Kidney Function in Older Adults in a Large Integrated Healthcare System: A Matched Cohort Study. J Am Geriatr Soc. 2016 Apr;64(4):798-805. https://pubmed.ncbi.nlm.nih.gov/27100576/

*Huttner et al (2018):* RCT showed that fosfomycin was inferior to nitrofurantoin re: clinical and microbiological resolution at 28 days[14].

*Concerns:*

- Resistance can be a problem with increased community use of fosfomycin and monitoring is a challenge as susceptibility testing is problematic and not widely available.
    - In a single study in Spain[15], resistance rates went from 2% to 22% in 5 years with extensive use of fosfomycin, increased by 50%. However, local susceptibility studies are needed to guide antibiotic management locally – which is generally lacking. A 2013 study in Gauteng[16] showed that 98.3% (95% CI 96.4% to 100%) of isolates were susceptible to fosfomycin (see below).
- Concomitant administration of antacids or calcium salts induces a significant reduction of fosfomycin therapeutically effective plasmatic and urinary concentrations, and should be avoided.

*Advantages:*

- Advantage is that for a single dose is required for uncomplicated UTI; but not indicated for severe pyelonephritis.
- Generally well tolerated with minor gastrointestinal intolerance (10%).
- Broad-spectrum antimicrobial (Gram positive and Gram negative) with no collateral damage.

**LOCAL SUSCEPTIBILITY DATA**

- Local high quality surveillance data relating to the organisms their susceptibilities for community acquired UTI is very limited, and should be considered a research priority as this would assist greatly to inform management going forward.
- Using available susceptibility data for *E. coli* isolates from antenatal clinics at four tertiary hospitals in Gauteng Province (2015-2019) as a proxy, just 39% of isolates were susceptible to trimethroprim/sulphamethoxazole, but 93% of isolates were susceptible to gentamicin, and ~93% were susceptible to nitrofurantoin. Fosfomycin susceptibility was not measured[17].
- Local susceptibility study done of community-acquired UTIs in Gauteng Province (2013)[16] showed that >90% of isolates were susceptible to fosfomycin and nitrofurantoin, though agents such as amoxicillin-clavulanate and trimethoprim/sulphamethoxazole did not –see table below:

| | GNB (*N*=181)* | | | |
|---|---|---|---|---|
| | Susceptibility | | $MIC_{50}$ | $MIC_{90}$ |
| Antimicrobial agent (*N*=9) | *n* | % (95% CI) | (mg/l) | (mg/l) |
| Ciprofloxacin | 170 | 93.9 (90.4 - 97.4) | 0.012 | 0.19 |
| Levofloxacin | 170 | 93.9 (90.4 - 97.4) | 0.023 | 0.38 |
| Norfloxacin | 170 | 93.9 (90.4 - 97.4) | 0.064 | 0.75 |
| Cefixime | 172 | 95.0 (91.8 - 98.2) | 0.25 | 0.75 |
| Cefuroxime | 169 | 93.4 (89.7 - 97.0) | 3 | 4 |
| Fosfomycin§ | 176 | 98.3 (96.4 - 100.0) | 0.5 | 4 |
| Nitrofurantoin§ | 155 | 90.6 (86.2 - 95.1) | 12 | 32 |
| Amoxicillin/clavulanic acid | 146 | 80.7 (74.9 - 86.5) | 6 | 16 |
| Trimethoprim/sulphamethoxazole | 75 | 41.4 (34.2 - 48.7) | >32 | >32 |

[14] Huttner A, Kowalczyk A, Turjeman A, et al. Effect of 5-Day Nitrofurantoin vs Single-Dose Fosfomycin on Clinical Resolution of Uncomplicated Lower Urinary Tract Infection in Women: A Randomized Clinical Trial. JAMA. 2018 May 1;319(17):1781-1789. https://pubmed.ncbi.nlm.nih.gov/29710295/

[15] Oteo J, Orden B, Bautista V, et al. CTX-M-15-producing urinary Escherichia coli O25b-ST131-phylogroup B2 has acquired resistance to fosfomycin. J Antimicrob Chemother. 2009 Oct;64(4):712-7. doi: 10.1093/jac/dkp288. Epub 2009 Aug 11. PMID: 19671590. https://pubmed.ncbi.nlm.nih.gov/19671590/

[16] Lewis DA, Gumede LY, van der Hoven LA, et al. Antimicrobial susceptibility of organisms causing community-acquired urinary tract infections in Gauteng Province, South Africa. S Afr Med J. 2013 Mar 15;103(6):377-81. https://pubmed.ncbi.nlm.nih.gov/23725955/

[17] NICD data on file

**SUMMARY**

| | Ciprofloxacin | Gentamicin | Cotrimoxazole | Nitrofurantoin | Fosfomycin | Amoxicillin/ clavulanic acid | Cephalosporin (e.g. cefuroxime) |
|---|---|---|---|---|---|---|---|
| **Local susceptibility** [16] (limited local data) | >90% | ?>90% | ~42% | >90% | >95% | ~80% | >90% |
| **Course** | 3 days, 12hrly | Single dose | 3-7 days, 12hrly | 5 days, 6hrly | Single dose | 3 days | 3 days |
| **Efficacy** (not in local setting) | Gold standard | Somewhat unclear but probably ~comparable ciprofloxacin | Equivalent to ciprofloxacin/ nitrofurantoin | Equivalent to other antimicrobials | Probably equivalent to other agents (but 1 RCT showed inferiority to nitrofurantoin) | Inferior microbiological clearance, but similar clinical efficacy | Unclear – cefpodoxime equivalent to cotrimoxazole (3 days each) |
| **Pros** | Efficacious | Low rate of usual side-effects with single dosing | | Mostly well-tolerated, no collateral damage | Single dose, well tolerated, no collateral damage | | Well tolerated |
| **Cons** | Side-effect profile poor, collateral damage | IM injection (painful), adjusted body weight dosing | Well tolerated | Single supplier, 6-hourly dosing | Single supplier, can't test/monitor resistance easily | Clearance lower, collateral damage | Collateral damage (ESBLs) |

**NEMLC MEETING OF THE 5 NOVEMBER 2020:**

**Recommendation:** Gentamicin, IM be considered first line option for non-pregnant patients with community acquired UTI with normal renal function. Gentamicin recommended for prescribing by nurse prescribers; and a pragmatic single IM dose of 160 mg recommended for all, irrespective of weight.

***Rationale:*** Limited evidence suggests that a single dose of IM gentamicin 160 mg was effective in treating UTI[9]. A dose of 1 mg/kg (lower than the usual standard dose typically used for Gram-negative infections) yields peak urinary concentrations exceeding 400 µg/ml.[6] This peak urinary concentration is 100 times that of the 2020 Clinical and Laboratory Standards Institute (CLSI) breakpoint for E.Coli (the minimum inhibitory concentration [MIC] breakpoint for gentamicin susceptibility in E.Coli is ≤4 µg/mL).[7] Mean urinary concentrations 48 hours after a daily dose of 3mg/kg gentamicin, measured 38.4µg/ml (more than 9 times that of the breakpoint for gentamicin).[8]

**Level of Evidence: Pharmacokinetic studies**