

**SOUTH AFRICAN PRIMARY HEALTHCARE LEVEL ESSENTIAL MEDICINES LIST
CHAPTER 8: KIDNEY AND UROLOGY CONDITIONS
NEMLC RECOMMENDATIONS FOR MEDICINE AMENDMENTS (2020)**

Medicine amendment recommendations, with supporting evidence and rationale are listed below. Kindly review the medicine amendments in the context of the complete kidney and urology chapter.

Note: The PHC eye chapter has been updated to align to previous NEMLC recommendations as well as the recent NEMLC-approved Adult Hospital Level STGs and EML, 2019 edition.

| SECTION | MEDICINE/MANAGEMENT | ADDED/DELETED/AMENDED/NOT ADDED/ RETAINED |
|---|----------------------|---|
| 8.4 Urinary tract infection (UTI): | | |
| - <i>Uncomplicated cystitis</i> | Ciprofloxacin, oral | Deleted |
| | Fosfomycin, oral | Added |
| | Gentamicin, IM | Added |
| | Nitrofurantoin, oral | Added |

8.4 URINARY TRACT INFECTION (UTI)

UNCOMPLICATED CYSTITIS

Ciprofloxacin, oral: *deleted*

Nitrofurantoin, oral: *added and indications extended to all uncomplicated UTI patients*

Fosfomycin, oral: *added and indications extended to all uncomplicated UTI patients*

Gentamicin, IM: *added, but not indicated in pregnancy and renal impairment (doctor prescribed)*

The PHC/Adult Expert review Committee reviewed the evidence for consideration of i) gentamicin, IM single dose for uncomplicated UTI in adults; ii) dosing of single-dose gentamicin IM at primary level of care.

1. Gentamicin, IM single dose for uncomplicated UTI in adults

Please refer to the medicine review, gentamicin for uncomplicated UTI (November 2019); as well as the evidence summary below:

- *Gentamicin, IM medicine review:*



Gentamicin for UTI-Adults Review_N

<http://www.health.gov.za/index.php/standard-treatment-guidelines-and-essential-medicines-list/category/286-hospital-level-adults>

- *Evidence summary of antimicrobials for community acquired UTI*



Antimicrobials for community acquired

<http://www.health.gov.za/index.php/standard-treatment-guidelines-and-essential-medicines-list/category/404-phc-medicines-reviews>

- **Price comparison:**

Prices for a single dose of fosfomycin, 5-day course of nitrofurantoin and single dose of gentamicin, IM 3mg/kg:

| Medicine | Treatment Regimen | Price (course)* | Unit price* | MSH PI (2015)** |
|----------------------|---|-----------------|-------------|-----------------|
| Fosfomycin, oral | 3 g as a single dose | R 120.77 | R120.77 | n/a |
| Nitrofurantoin, oral | 100 mg 6 hourly for 5 days (20 capsules) | R 101.38 | R5.07 | R3.52 |
| Gentamicin, IM | >70 kg, 240mg (i.e. 3x80mg/2ml = 6 ml in total) | R 19.41/6ml | R6.47 | R2.06 |
| Gentamicin IM | ≤70kg, 160mg (i.e. 2x80mg/2ml = 4 ml in total) | R 12.94/4ml | R6.47 | R2.06 |

*Contract circular HP02-2019AI: Nitrofurantoin 100 mg, 50 capsules = R 253.44; Fosfomycin 3g, sachet = R 120.77; Gentamicin 80mg/2ml=R6.47 (accessed 2 November 2020)

Note: Confirmed with Pharmicare that the tender price is correct and for the 100mg dose of nitrofurantoin; the buy-out price for the 50mg dose of nitrofurantoin, 50 capsules is R326.49) – email on file.

** MSH International Medicine Products Price Guide, 2015: <https://www.msh.org/resources/international-medical-products-price-guide>

- Median buyer price - Nitrofurantoin 100 mg: US\$ 0.2103; Gentamicin 40mg/ml:US\$0.0616 (80mg/2ml=US\$0.1232)

- Lowest buyer price - Nitrofurantoin 100 mg: US\$ 0.0216 [CIF]; Gentamicin 40mg/ml: US\$0.0233 (80mg/2ml=US\$0.0466)

(Oanda average exchange rate, 108 days, accessed 2 November 2020: US\$1 = ZR16.74 - <https://www.oanda.com/fx-for-business/historical-rates>)

Recommendation: The PHC/Adult Hospital Level Committee recommended that gentamicin, IM as a single dose be considered for uncomplicated UTI in adults at primary level of care, as first line option (except in chronic or known renal impairment and pregnancy). Fosfomycin, oral be considered as second-line option followed by nitrofurantoin, oral. Furthermore, the Committee strongly recommends advocacy and price negotiations for fosfomycin and nitrofurantoin.

Rationale:

- There is limited RCT evidence, available aminoglycosides studied for uncomplicated UTI in adults includes netilmicin¹ and amikacin²; whilst gentamicin has only been studied in paediatrics^{3 4 5}. However, the PHC/Adult Hospital Level Committee was of the opinion that the available evidence⁶ suggests a therapeutic aminoglycoside effect. Aminoglycosides is not a current global practice for management of uncomplicated UTI (but was recommended historically in the 1970's-1980's). Going forward, local antimicrobial susceptibility data for community acquired UTI is required to inform decision-making. Single dose gentamicin is considered to be a more pragmatic option, as amikacin is preferred for nosocomial infections.
- Intramuscular injections are painful with a relatively large volume requiring administration. The risk of occupational injury was also considered. However, it was noted that ceftriaxone, IM is part of dual therapy for syndromic management of STI at primary level of care. The PHC/Adult Hospital Level Committee was of the opinion that management of a single dose of antibiotic was more acceptable amongst primary level healthcare workers.
- Administration in the obese patient was also a concern; and gentamicin is contra-indicated in pregnancy.
- The supply constraints of nitrofurantoin and fosfomycin (both sourced from single suppliers) was a concern.
- Gentamicin, IM administered as a single dose is more affordable compared to fosfomycin and nitrofurantoin (see table above).

II. Dosing of gentamicin, IM single at primary level of care

Please refer to the evidence summary, below:



Gentamicin dosing for community acqu

<http://www.health.gov.za/index.php/standard-treatment-guidelines-and-essential-medicines-list/category/404-phc-medicines-reviews>

Recommendation: Based on the evidence summary above, the PHC/Adult Hospital Level Committee deliberated on the following options:

¹ Bailey RR, Blake E, Peddie BA. Comparison of single dose netilmicin with a five-day course of co-trimoxazole for uncomplicated urinary tract infections. N Z Med J. 1984 Apr 25;97(754):262-4. <https://pubmed.ncbi.nlm.nih.gov/6374533/>

² Rocca Rossetti S. Single-shot vs conventional therapy with amikacin for treatment of uncomplicated urinary tract infections: a multicenter study. Chemioterapia. 1986 Dec;5(6):394-9. PMID: 3802301. <https://pubmed.ncbi.nlm.nih.gov/3802301/>

³ Varese LA, Grazioli F, Viretto A, et al. Single-dose (bolus) therapy with gentamicin in management of urinary tract infection, Int J Pediatr Nephrol, 1980. 1:104. [https://www.jpeds.com/article/S0022-3476\(01\)64161-1/abstract](https://www.jpeds.com/article/S0022-3476(01)64161-1/abstract)

⁴ Grimwood K, Abbott GD, Fergusson DM. Single dose gentamicin treatment of urinary infections in children. N Z Med J. 1988 Aug 24;101(852):539-41. PMID: 3045718. <https://pubmed.ncbi.nlm.nih.gov/3045718/>

⁵ Khan AJ, Kumar K, Evans HE. Single-dose gentamicin therapy of recurrent urinary tract infection in patients with normal urinary tracts. J Pediatr. 1987 Jan;110(1):131-5. <https://pubmed.ncbi.nlm.nih.gov/3794874/>

⁶ 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. 2018 Dec 21;63(1). pii: e02165-18. <https://www.ncbi.nlm.nih.gov/pubmed/30397061>

- 1) Gentamicin 3mg/kg IM as a single dose
- 2) Gentamicin 3mg/kg IM as a single dose, with weight adjusted dosing for the obese patient.
- 3) Fixed doses: ≤ 70 kg 160mg; >70 kg 240 mg – as a single dose.

The PHC/Adult Hospital Level Committee recommended that fixed dosing of IM gentamicin (option 3) be considered for uncomplicated UTI in adults. However, concerns were raised about IM dosing in obese patients, as the needle may not penetrate to the depth of the muscle. Acceptability amongst healthcare workers and patients is also unknown, and may need to be investigated.

Level of Evidence: III Expert opinion

However, at the NEMLC meeting of 5 November 2020, NEMLC reviewed and finalised the dose of gentamicin, IM as a single dose – see below:

NEMLC MEETING OF 5 NOVEMBER 2020:

Dosing: Gentamicin dosed at 5mg/kg was generally used in severe infections (e.g. pyelonephritis). However, gentamicin is highly concentrated in urine and renal tissue and curing UTIs is related moreso to achieving antimicrobial inhibitory urinary levels rather than serum levels⁷. Therefore, a lower dose of 160 mg as a single dose is adequate in lower UTI, where there is no evidence of renal impairment. For lower urinary tract infection, a Canadian package insert⁸ recommends a single dose 160mg gentamicin IM to patients with normal renal function, and for patients weighing <60 kg, a single dose of 3 mg/kg. After much deliberation, the NEMLC recommended that for pragmatic purposes, the dose of gentamicin be recommended as 160mg as a single IM dose.

Data: There is a paucity of data to inform antimicrobial management of community acquired UTIs. National Health Laboratory Services (NHLS) antenatal data from four tertiary hospital was used as a proxy. However, despite *E. coli* being the most representative microorganism isolated from community and hospital acquired UTI; resistant patterns are very different. Data was reported to be forthcoming from the Western Cape for community acquired UTI, yet to be published.

Cefuroxime: Cefuroxime may be a reasonable option, but is currently not listed on the EML and indication creep was a concern (to be added to the summary document on antimicrobial for UTI)

NEMLC 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^{2,3}. 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/ml⁹. 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)¹⁰. 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)¹¹

Level of Evidence: Pharmacokinetic studies

⁷ Stamey, T. A., D. E. Govani and J. M. Palmer. 1965. The localization and treatment of urinary tract infections: the role of bactericidal urine levels as opposed to serum levels. *Medicine (Baltimore)*. 1965 Jan;44:1-36. <https://pubmed.ncbi.nlm.nih.gov/14264351/>

⁸ Sandoz Canada Inc. Product monograph: ^PrGentamicin Injection USP, 29 August 2017. <https://www.sandoz.ca/sites/www.sandoz.ca/files/Gentamicin%20Inj%20Product%20Monograph.pdf>

⁹ Bennett JE, Dolin R, Blaser MJ. 2015. Mandell, Douglas, and Bennett's principles and practice of infectious diseases. Elsevier/Saunders, Philadelphia, PA

¹⁰ CLSI. 2020. Performance standards for antimicrobial susceptibility testing, 30th ed. CLSI document M100. Clinical and Laboratory Standards Institute, Wayne, PA

¹¹. Fang GD, Brennen C, Wagener M, Swanson D, Hilf M, Zadecky L, DeVine J, Yu VL. 1991. Use of ciprofloxacin versus use of aminoglycosides for therapy of complicated urinary tract infection: prospective, randomized clinical and pharmacokinetic study. *Antimicrobial Agents and Chemotherapy*.35:9, 1849-1855