

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

EVIDENCE SUMMARY

Date: 13 October 2020

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QUESTION: Intramuscular gentamicin for treatment of uncomplicated urinary tract infections - what dose should be used

Single dose therapy with gentamicin was recently selected by NEMLC as the treatment of choice for uncomplicated urinary tract infections. A gentamicin intramuscular (IM) dose of 5mg/kg of body weight was suggested, based on the recommendation of a 2018 systematic review of evidence for single-dose aminoglycosides for treatment of urinary tract infections.¹ The justification for the upper end of the dose range (i.e. 5mg/kg dose) recommended in this review, was to ensure high urinary peak concentrations of gentamicin.

However, concerns were raised that 5 mg/kg dosing would require large volumes to be administered intramuscularly. For example: a 70 kg adult would require a 350 mg dose which equates to 8.75 mL, as 4 – 5 ampoules (80 mg/2 mL) are required. There may be associated pain on administering a large volume of IM gentamicin. Intramuscular gentamicin injections are generally well tolerated; however, there are reports of pain or local irritation at the injection site.²

Recommended single-dose gentamicin in mg/kg

The systematic review included three, small, paediatric studies, all of which assessed the efficacy of single-dose gentamicin for the treatment of urinary tract infection in patients. The dosages used in each study were 5 mg/kg, 3 mg/kg, and 5 mg/kg up to a maximum dose of 300mg respectively.^{3,4,5} Two studies included patients with initial or recurrent episodes of urinary tract infections.^{3,4} One study included patients with only recurrent urinary tract infections.⁵ One study did not report on whether the infection involved the upper or lower urinary tract, one study included patients with upper or lower urinary tract infections, and one study included patients with only lower urinary tract infections.^{3,4,5}

Limitations of the review include - all three referenced studies were conducted before 1990, and all are based on a paediatric-only population – this is a key point as drug exposures in children given the same mg/kg dose will be lower than they are in adults, therefore the adult equivalent dose to 5 mg/kg gentamicin would be lower. Two of the three studies included patients with urinary tract malformations, and do not fulfil the criteria of an uncomplicated urinary tract infection.^{3,4}

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

Weight-adjusted dosing of gentamicin in obese, adult patients

Weight-adjusted dosing of gentamycin in obesity is complex. A pragmatic and feasible recommendation to assist with ease of administering intramuscular gentamicin, is to simplify the 3mg/kg dose by using fixed-dosing:

- adult weighing >70 kg, 240mg of gentamicin is recommended (i.e. 3 ampoules, 6 ml in total)
- adult weighing ≤70kg, 160mg of gentamicin is recommended (i.e. 2 ampoules, 4 ml in total)

Recommendation

Based on above findings, 3mg/kg (i.e. the lower end of the dose range of 3-5mg/kg) with a maximum dose of 240mg of gentamicin as a single dose intramuscularly, is recommended. Fixed-dosing for obese patients, i.e. 240mg if weight >70 kg, and 160mg if weight ≤70kg, is recommended.

Level of Evidence: II Systematic review (extrapolated from paediatric studies)

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

- 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 Committee proposed 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.

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 UTI⁹. 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

References:

- 1) Goodlet KJ, Benhalima FZ, Nailor MD. 2018. A Systematic Review of Single-Dose Aminoglycoside Therapy for Urinary Tract Infection: Is It Time To Resurrect an Old Strategy? *Antimicrobial Agents and Chemotherapy*. 63:1
- 2) APP, Fresenius Kabi USA. Gentamicin Package Insert. 2013
- 3) Varese LA, Grazioli F, Viretto A, Antoniola P. 1980. Single-dose (bolus) therapy with gentamicin in management of urinary tract infections. *Int J Pediatr Nephrol* 1:104 –105
- 4) Grimwood K, Abbott GD, Fergusson DM. 1988. Single dose gentamicin treatment of urinary infections in children. *N Z Med J* 101:539 –541.
- 5) Khan AJ, Kumar K, Evans HE. 1987. Single-dose gentamicin therapy of recurrent urinary tract infection in patients with normal urinary tracts. *J Pediatr* 110:131–135. [https://doi.org/10.1016/S0022-3476\(87\)80308-6](https://doi.org/10.1016/S0022-3476(87)80308-6).
- 6) Bennett JE, Dolin R, Blaser MJ. 2015. *Mandell, Douglas, and Bennett's principles and practice of infectious diseases*. Elsevier/Saunders, Philadelphia, PA
- 7) CLSI. 2020. *Performance standards for antimicrobial susceptibility testing, 30th ed.* CLSI document M100. Clinical and Laboratory Standards Institute, Wayne, PA.
- 8) 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
- 9) Labovitz E, Levison ME, Kaye D. Single-dose daily gentamicin therapy in urinary tract infection. *Antimicrob Agents Chemother*. 1974 Oct;6(4):465-70.