South African National Essential Medicine List
Adult Hospital Level Medication Review Process
Component: Nephrology

MEDICINE REVIEW

1) Executive Summary

Date: 14 November 2019
Medicine (INN): Gentamicin, IM
Medicine (ATC): J01GB03
Indication (ICD10 code): Uncomplicated urinary tract infection (UTI) (N30.9/O23.4/N10)
Patient population: Adults
Prevalence of condition: Life time prevalence about 20% (D A Lewis et al 2013).
Level of Care: Secondary level (Hospital)
Prescriber Level: Medical officers
Current standard of Care: Ciprofloxacin
Efficacy estimates: (preferably NNT) *Gentamicin IM vs comparator (oral fosfomycin, trimethoprim/ sulfamethoxazole, amoxicillin, cephalosporin) (Goodlet et al, 2018):*

- Pooled microbiologic cure rate: 94.5% vs 4.3%.
- Cure was sustained (no recurrence) for 73.4% vs 9.6% of patients at day 30.
- Lower cure rates among patients with radiographic urinary tract abnormality
- 63/13,804 (0.5%) ADRs reported (nephrotoxicity, vestibular toxicity, injection site reaction, but no hearing loss observed).

Motivator/reviewer name(s): Dr R Kaswa, Dr H Dawood, Ms TD Leong
PTC affiliation: Dr H Dawood: KZN Provincial PTC

2) Name of author(s)/motivator(s)

Primary reviewer: Dr R Kaswa
Secondary reviewe(s)r: Dr H Dawood, Ms TD Leong

3) Author affiliation and conflict of interest details

Dr R Kaswa

- *Affiliation:* Mthatha Regional Hospital, Adult Hospital Level Committee (2017-2020); no conflicts of interest declared.

Dr H Dawood:

- *Affiliation:* Greys hospital, KZN Department of health; Caprisa, UKZN; Adult Hospital Level Committee (2017-2020). *Conflict of interests:* MSD: ECMID 2018 - Conference attendance; ACTA study - DSMB member (crypto meningitis); Adcock Ingram - HIV discussion with general practitioners; President elect: IDSSA; SA HIV Clinician Society Cryptococcal meningitis Guidelines.

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4) Introduction/ Background

Community-acquired urinary tract infection (UTI) is a common medical condition affecting up to 20% of women sometime in their lifetime(1). Urinary tract infection (UTI) is a common indication for antibiotic prescribing across both inpatient and outpatient settings.). UTIs are most commonly caused by Enterobacteriaceae and other Gram-negative organisms (figure 1). However, antibiotic resistance rates among uropathogens to first-line agents is increasing(2).

The recent warnings of the risk of serious adverse events associated with fluoroquinolone use in previously healthy persons, prompts consideration of any decision to prescribe quinolones and fluoroquinolones. The decision to use this medicine should be taken after a careful assessment of the benefit and risks and other appropriate options that are available. NEMLC raised concerns regarding serious side effects associated with extended use of empirical fluoroquinolone therapy for uncomplicated UTI(3).

Over the past several decades, aminoglycosides have maintained excellent clinical activity against the majority of uropathogens, including drug-resistant *Enterobacteriaceae*. Aminoglycosides are eliminated in their active form, exclusively by the renal route, but the main concern has been toxicities associated with multiday administration, of aminoglycoside(1).
The administration of single dose aminoglycoside for UTI treatment is advantageous in the outpatient setting. This eliminates the need for patient adherence, (non-adherence rates approach 60%), and may avert the need for inpatient admission due to the lack of susceptible oral antibiotic options.

Aminoglycosides are an ideal drug class for single-dose treatment of UTI, as they are excreted in high concentrations in the urine, and exceed up to 100-fold plasma concentrations within an hour after parenteral administration(2)(5).A dose of 1 mg/kg of gentamicin (will yield peak urine concentrations > 400 g/ml , 100 times the 2018 Clinical and Laboratory Standards Institute (CLSI) breakpoint for Enterobacteriaceae and far exceeding the peak-to-MIC ratio of 10 to 12 that is recommended for efficacy. Additionally, after a single dose, concentrations remain above therapeutic levels for most uropathogens for 72 h or longer(4)(5). Thus, the objective of this review was to explore the efficacy of single-dose aminoglycoside therapy for the treatment of UTI.

Severe symptomatic UTI was defined as the clinical syndrome of fever, bacteriuria, pyuria and - beyond infancy - symptoms of UTI (flank pain, dysuria). Patients with severe symptomatic UTI, supposedly pyelonephritis, were included. Studies that included only patients with mild UTI (cystitis) were excluded. Complicated UTI was defined as UTI in patients with pre-existing complicating kidney disease such as obstruction, neurogenic bladder, chronic catheterisation. Patients with complicated UTI were excluded under the assumption that the underlying bacterial spectrum is different to that of uncomplicated severe UTI.

Cure rates were defined as no clinical signs, or bacteriological cure rate defined as eradication of bacteria,and combined clinical and bacteriological cure rate defined as no clinical signs and eradication of bacteria.

5) Purpose/Objective i.e.

P- patients with uncomplicated UTI
I – gentamicin, IM
C – Standard of care (ciprofloxacin, oral; amoxicillin/clavulanic acid, oral; nitrofurantoin, oral)
O - Clincal cure rates (defined as no clinical signs, bacteriological cure rate defined as eradication of bacteria, combined clinical and bacteriological cure rate defined as no clinical signs and eradication of bacteria)

6) Methods:

a) Data sources: Cochrane library, Pubmed, Google scholar.

Search restricted to systematic reviews and randomised controlled trials directly comparing gentamicin or aminoglycoside to standard of care for UTI. (If these are unavailable in the published literature, cohort studies, clinical guidelines, and case series to be reviewed in accordance with grading as per SORT criteria). Limited to published literature; grey literature not included.

b) Search strategies:

Cochrane Library: "gentamicin" in All Text AND Uncomplicated urinary tract infection in All Text AND adults in Title Abstract Keyword - in Cochrane Reviews (Word variations have been searched).
Two reviews retrieved, both rejected (1 was not relevant to the PICO question; the other reviewed *"amikacin 15 mg/kg/d or gentamicin 3 mg/kg/d with ampicillin 100 mg/kg/d for 7 to 10 days"*).

Pub Med: (("gentamicins"[MeSH Terms] OR "gentamicins"[All Fields] OR "gentamicin"[All Fields]) AND ("adult"[MeSH Terms] OR "adult"[All Fields] OR "adults"[All Fields])) AND (uncomplicated[All Fields] AND ("urinary tract infections"[MeSH Terms] OR ("urinary"[All Fields] AND "tract"[All Fields] AND "infections"[All Fields]) OR "urinary tract infections"[All Fields] OR ("urinary"[All Fields] AND "tract"[All Fields] AND "infection"[All Fields]) OR "urinary tract infection"[All Fields]))

20 articles retrieved, and all excluded as not relevant to PICO question.

Google scholar: "gentamicin" or "aminoglycoside" and "urinary tract infection" or "UTI".
1 article was retrieved – see evidence synthesis table below.

d) **Evidence synthesis**

Author, date	*Type of study*	N	Population	Comparators	Primary outcome(s)	Efficacy of single dose	Comments
Goodlet, et al, 2018 (2)	Systematic review	13 studies (n=13804)	Both inpatient (6/13) and outpatient (10/13) populations were represented. Across all studies, patient ages ranged from 2 weeks to 70 years. The majority of studies included children only (53.8%), 3 RCTs in adults (including 1 exclusively in elderly patients [mean age, 74 years]), 1 including both children and adults, and 1 not reporting age. Females represented 79.5% of all patients.	Aminoglycosides (Netilmicin, amikacin and gentamicin) administered IM vs comparators (single oral dose of fosfomycin; 5 to 10 days of oral trimethoprim/ sulfamethoxazole, amoxicillin, cephalosporin) or placebo	**Microbiologic cure** (documented eradication of bacteria from the urine within 7 days of antibiotic administration). **Clinical cure** (resolution of UTI signs and symptoms (e.g., dysuria and frequency)). **Reinfection** (UTI recurrence on day 15 to 30 after therapy and/or documentation that the infecting organism differed from the organism associated with the index infection). **Relapse** (UTI recurrence on day 1 to 14 posttherapy not meeting the definition for reinfection. Recurrences represent any new UTI within 30 days of the index	Microbiologic cure rates were able to be determined for 11/13 studies. All were in excess of 85%, with an overall cure rate of 94.5% ±4.3%. Only 2 studies reported clinical cure, with rates of 82.8% and 94.7%. Among the studies with a minimum of 30 days follow-up, an overall 19.0% (84/443) 30-day recurrence rate was reported, with roughly equal numbers of relapses and reinfections. Among the studies with adequate data, the percentage of patients with sustained microbiologic cure at 30 days was 73.4% ±9.6%. Among the studies providing comparisons of cure rates for patients with and without urinary tract abnormalities, patients with anatomical abnormalities were less likely to have initial microbiologic cure (86.3% versus 96.9%, P < 0.01), and, among studies with adequate data, were less likely to have sustained microbiologic cure at 30 days (57.3% versus 87.5%, P < 0.001). There was no significant difference in microbiologic cure rate in a comparison of pediatric-only studies and adult-only studies (95% microbiologic cure rate and 94% microbiologic cure rate, respectively; P<0.05). There were inadequate data to compare sustained cure rates. Only one study of children age 5 to 15 years stratified efficacy data by sex, with a 9.8% 3-year	More local studies needed to evaluate the performance of single dose aminoglycoside therapy against modern uropathogens, which may have elevated aminoglycoside MICs. One study of gentamicin monotherapy for acute pyelonephritis, two-thirds of inpatients with infection caused by gentamicin-resistant *Enterobacteriacea*e had early clinical success at 72 hrs (n=32), suggesting that aminoglycoside therapy may be effective for many UTI patients even with MICs above the breakpoint, either due to enhanced drug concentrations even within the upper urinary tract or due to spontaneous immune-mediated clearance of infection. An additional limitation is that symptom data were lacking, and clinical cure was infrequently evaluated; thus, some patients may not have had a true UTI. No studies compared single-dose aminoglycoside therapy to other antibiotic therapies, currently recommended (i..e nitrofurantoin, fosfomycin). . Several of the comparator antibiotics are also not frequently used in current practice due to resistance (e.g., oral amoxicillin), and these comparisons were unblinded and may have been underpowered.

					infection, i.e., the sum of relapses and reinfections).		

a) Evidence quality: Limited evidence with one systemic review of RCTs that are small and of low to moderate methodological quality.

7) Discussion:

Aminoglycosides are a well-established class of antibiotics that are especially useful in the treatment of serious infections caused by Gram-negative bacteria due to their rapid, concentration-dependent bactericidal action and ability to act synergistically with other antibiotics. Although the use of aminoglycosides has declined over the years due to concerns about toxicity, they have recently re-emerged as a practical approach to treating patients with UTIs caused by MDR Gram-negative bacteria. Ideally, aminoglycosides are dosed once daily, a treatment strategy that has been shown to reduce toxicity while maintaining efficacy compared with multiple daily doses(4)(6). However, data from large, prospective randomized controlled trials evaluating the safety and efficacy of once-daily aminoglycosides in UTIs are limited.

Available evidence of low to moderate quality, suggests that aminoglycosides have good microbiological cure rate with low number of report ADRs associated with single IM dose for uncomplicated UTI.

A single-dose aminoglycoside therapy for UTI has observed high (87 to 100%) microbiologic cure rates, with the majority of patients experiencing no recurrence of infection within 30 days, supporting the feasibility of single dose therapy as a therapeutic strategy. These results were observed in both inpatient and outpatient settings. While dosing strategies varied across the studies, doses at the upper end of those used in the included studies (5 mg/kg of body weight for gentamicin or tobramycin and 15 mg/kg for amikacin) are recommended.

Although aminoglycosides do have a role in expanding empirical Gram-negative coverage for select inpatient conditions, use as monotherapy is predominantly limited to genitourinary conditions. Thus, increased incorporation of aminoglycosides into UTI treatment algorithms may be an effective fluoroquinolone sparing strategy(4).

Aminoglycoside therapy is associated with adverse drug reactions, including nephrotoxicity, hearing loss, vestibular toxicity, and rare neuromuscular blockade. Although the potential for these events should be recognised, nephrotoxicity rarely develops with short aminoglycoside courses of 3 days or fewer, even at high doses, and is mostly reversible. Common non drug-related causes of acute kidney injury (e.g., intravascular volume depletion) should also be considered. In a systematic review of 24,107 patients receiving a single gentamicin dose, only 1.6% experienced transient serum creatinine elevations, with no rises in serum creatinine reported for studies where all patients were less than 75 years of age.

Thus, routine laboratory or auditory monitoring following single-dose therapy does not appear to be indicated in the absence of significant patient risk factors, particularly in younger, otherwise-healthy patients. However, selection of an alternative regimen for patients with significant renal impairment may be advisable due to a lack of data for this population.

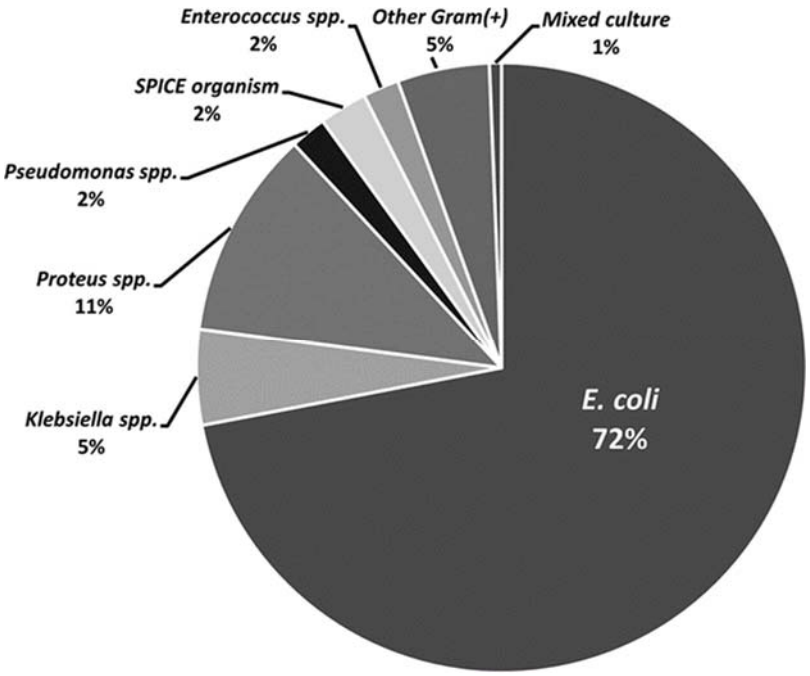

Figure 1: Distribution of bacteria from urine cultures. SPICE organism, any of the following: Serratia spp., Providencia spp., Morganella spp., Citrobacter spp., or Enterobacter spp
(Source: Goodlet KJ, Benhalima FZ, Nailor MD. A Systematic Review of Single-Dose Aminoglycoside Therapy for Urinary Tract Infection: Is It Time To Resurrect an Old Strategy? Antimicrob Agents Chemother. 2018 Dec 21;63(1). pii: e02165-18).

Summary: Available evidence provides support for single-dose aminoglycoside therapy as a plausible treatment for UTI. Single-dose aminoglycoside therapy is a promising strategy deserving of enhanced consideration in the current era of multidrug resistance and patient non-adherence.

EVIDENCE TO DECISION FRAMEWORK

	JUDGEMENT	SUPPORTING EVIDENCE & ADDITIONAL CONSIDERATIONS
QUALITY OF EVIDENCE	**What is the overall confidence in the evidence of effectiveness?** Confident [X] Not confident [ ] Uncertain [ ]	
BENEFITS & HARMS	**Do the desirable effects outweigh the undesirable effects?** Benefits outweigh harms [X] Harms outweigh benefits [ ] Benefits = harms or Uncertain [ ]	
THERAPEUTIC INTERCHANGE	Therapeutic alternatives available: Yes [X] No [ ] List the members of the group: Fosfomycin; nitrofurantoin List specific exclusion from the group: n/a	Rationale for therapeutic alternatives included: Local susceptibility study done in Gauteng showed that uropathogens were susceptible to fosfomycin, nitrofurantoin. References: Lewis et al, 2013 (1)
VALUES & PREFERENCES / ACCEPTABILITY	**Is there important uncertainty or variability about how much people value the options?** Minor [ ] Major [ ] Uncertain [X] **Is the option acceptable to key stakeholders?** Yes [ ] No [ ] Uncertain [X]	
RESOURCE USE	**How large are the resource requirements?** More intensive [ ] Less intensive [X] Uncertain [ ]	Price of medicines/ treatment course: **Medicine** / **Cost (ZAR)*** Gentamicin 80 mg inj: 6.19 Fosfomycin 3g: 103.26 Nitrofurantoin 100 mg, 6 hourly for 5 days = (20 x 100 mg capsules): 99.61 * Contract circular: HP02-2019AI **Additional resources:** n/a
EQUITY	**Would there be an impact on health inequity?** Yes [ ] No [X] Uncertain [ ]	
FEASIBILITY	**Is the implementation of this recommendation feasible?** Yes [X] No [ ] Uncertain [ ]	

Type of recommendation	We recommend against the option and for the alternative	We suggest not to use the option or to use the alternative	We suggest using either the option or the alternative	We suggest using the option	We recommend the option
	☐	☐	☒	☐	☐

Recommendation

Based on this evidence review, is the Adult Hospital Level Committee recommends that gentamicin, IM 5mg/kg as a single dose as an alternative to ciproflxacin; whilst in pregnancy and renal impairment, fosfomycin and nitrofurantoin may be considered.

Rationale: Meta-analysis (Goodlet et al, 2018) of RCTs investigating upper or lower UTI, as well as initial or recurrent infections showed acceptable microbiological cure rate of single dose aminoglycosides for uncomplicated UTI with minimal toxicity. Single dose gentamicin considered to be a more pragmatic option, as amikacin is preferred for nosocomial infections. It is acknowledged that uncomplicated UTI has a substantial spontaneous cure rate, but morbidity is being managed in this setting.

Local susceptibility data from NICD/NHLS, though sourced from antenatal care centre at a tertiary institution (Charlotte Maxeke Hospital), showed resistance of *E.Coli* to ciprofloxacin (7); similar to results of susceptibility study of community acquired UTI also done in Gauteng (Lewis et al, 2013).

Level of Evidence: II Metaanalysis of RCTs of low to moderate quality, Antibiotic susceptibility study and data, Expert opinion

Review indicator:

Evidence of efficacy	Evidence of harm	Price reduction
X	X	

VEN status:

Vital	Essential	Necessary
	X	

NEMLC MEETING OF 5 DECEMBER 2019:

NEMLC ratified the medicine review, and accepted the proposal as recommended by the Adult Hospital Level Committee, above.

Monitoring and evaluation considerations

Research priorities

Surveillance of community acquired UTI throughout the country

References:

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