

Single-Dose Aminoglycosides for UTIs

Introduction

1. UTIs are most commonly caused by *Enterobacteriaceae* (**E. coli**, *Proteus spp.*, *Klebsiella spp.*, etc.) and other Gram-negative organisms.
2. UTIs are classified based on risk factors (uncomplicated vs. complicated) and the area of the urinary tract affected (cystitis vs. pyelonephritis). #
3. **Treatment of asymptomatic bacteriuria is often not beneficial** and only supported by guidelines in pregnant women and before urological procedures that compromise the mucosa.
4. Inappropriate antibiotic use has led to **increased resistance in uropathogenic bacteria**.
5. **Barriers to traditional oral antibiotic therapy** include increasing bacterial resistance, nonadherence rates approaching 60%, and medication access issues.

Pharmacology			
Rationale:			
<ul style="list-style-type: none"> ✓ Excellent activity against most uropathogens, including drug-resistant <i>Enterobacteriaceae</i> ✓ Eliminated as active drug almost exclusively by the kidneys with concentrations 100-fold greater in the urine than plasma ✓ Post-antibiotic effect of aminoglycosides may persist for up to 72 hours ✓ Toxicities may be limited with one-time administration ✓ Prevents medication access & adherence concerns 			
	Gentamicin	Amikacin	Tobramycin
	5 mg/kg IV/IM once	15 mg/kg IV/IM once	5 mg/kg IV/IM once
Dose	<ul style="list-style-type: none"> ▪ Underweight [TBW<IBW]: use TBW ▪ Nonobese [TBW 1x to 1.25x IBW]: use IBW or TBW ▪ Obese [TBW >1.25x IBW]: use adjusted body weight 		
Administration	IM: undiluted 40 mg/mL vial IV: Dilute in 50 to 200 mL of NS, LR, or D5W and infuse over 30 min to 2 h	IM: use undiluted 500 mg/2 mL vial IV: Dilute in 100 to 200 mL of NS, LR, or D5W and infuse over 30 min to 60 min	IM: use undiluted 80 mg/2 mL vial IV: Dilute in 50 to 100 mL of NS, LR or D5W and infuse over 20 min to 60 min
PK/PD	-IM: rapid & complete absorption -No CYP-mediated metabolism -Urine (≥70% unchanged drug)	-IM: rapid & complete absorption -No CYP-mediated metabolism -Urine (94-98% unchanged drug)	-IM: rapid & complete absorption -No CYP-mediated metabolism -Urine (90-95% unchanged drug)
Adverse Effects	<ul style="list-style-type: none"> ▪ <u>Nephrotoxicity</u> ▪ <u>Ototoxicity</u> 		
Considerations	<ul style="list-style-type: none"> ▪ Caution in renal impairment ▪ <u>Large volume for IM administration</u> 		

#Definitions

Uncomplicated – non-pregnant women with no known anatomical and functional abnormalities of the urinary tract or comorbidities

Complicated – all men, pregnant women, anatomical or functional abnormalities of the urinary tract, indwelling urinary catheters, renal diseases, and/or other immunocompromising diseases such as diabetes

Cystitis – infection confined to the bladder; symptoms of increased urinary urgency, frequency & dysuria

Pyelonephritis – infection extends beyond the bladder; cystitis symptoms + fever, chills, flank & pelvic pain

Overview of Evidence

Study	Goodlet et al. 2018	
Design	Systematic review (n=13,804 patients across 13 studies published from 1978 to 1991)	
Included Studies	<p>-Single-dose aminoglycoside with no concomitant antibiotic therapy</p> <p>-Average patient: pediatric female with acute uncomplicated cystitis secondary to E.coli with normal renal function treated in the outpatient setting</p> <p>-7 studies with a comparator arm:</p> <ul style="list-style-type: none"> ▪ Single dose oral fosfomycin ▪ Oral trimethoprim-sulfamethoxazole, amoxicillin, or cephalosporin x 5-10 days <p>-72% of isolates were E. coli</p> <p>-Netilmicin was the most commonly used aminoglycoside, followed by amikacin and gentamicin</p>	
Outcomes	<p>-Overall microbiologic cure rate of 94.5% ± 4.3%</p> <ul style="list-style-type: none"> ▪ No differences between pediatric- and adult-only studies ▪ No differences between aminoglycosides and comparator arms ▪ Patients with anatomical abnormalities were less likely to have initial microbiologic cure <p>-Overall 19% (84/443) 30-day recurrence rate in studies that had minimum 30-day follow-up</p> <p>-Only 0.5% (64/13,804) reported adverse effects, mainly due to vestibular toxicity (53 patients) and nephrotoxicity (7 patients)</p>	
Limitations	<p>-Majority of patients (13,258/13,804) were from one study</p> <p>-Generalizability is questionable</p> <ul style="list-style-type: none"> ▪ 8 studies (pediatric only) & 3 studies (adults only) ▪ Only 1 study included patients with moderate or severe renal impairment (10/44 patients) ▪ Only 2 studies included patients with pyelonephritis ▪ No cases of sepsis or bacteremia were reported <p>-Older studies</p> <ul style="list-style-type: none"> ▪ Did not study against modern uropathogens ▪ Did not compare to commonly used agents, such as nitrofurantoin or IV ceftriaxone <p>-Did not assess for future uropathogen resistance</p> <p>-Symptom data was not reported</p> <ul style="list-style-type: none"> ▪ Patients could have been treated for asymptomatic bacteriuria ▪ Lack of assessment of clinical cure rate for majority of studies <p>-No studies were blinded</p> <p>-Unknown drug dosing of comparator arms</p>	
The Bottom Line	<p><u>Consider use in patients with:</u></p> <ul style="list-style-type: none"> ▪ Lower urinary tract infection (cystitis), ▪ No systemic signs/symptoms, ▪ Normal renal function, and ▪ No urinary tract abnormalities 	<p><i>AND multiple of the following:</i></p> <ul style="list-style-type: none"> ▪ Medication access issues ▪ Known medication nonadherence ▪ Multiple antibiotic allergies ▪ Known history of resistant organisms ▪ Unable to take oral medications

Conclusions

1. Single-dose aminoglycoside therapy may be a plausible treatment option in patients with cystitis.
2. Aminoglycosides can be administered either the IV or IM route, and therefore, does not necessarily require IV access. Gentamicin may be considered the preferred aminoglycoside based on frequency of use in studies.
3. The risk for adverse events with single-dose aminoglycosides is low, however, there are concerns for nephrotoxicity and ototoxicity.
4. Single-dose aminoglycoside should NOT be recommended as first-line therapy. It can be considered in patients with acute cystitis with normal renal function and multiple barriers to the standard of care.

References

1. Bonkat G, Bartoletti RR, Bruyere F et al. EAU Guidelines on Urological Infections. *Urological Infections*. 2019.
2. Uncomplicated Cystitis and Pyelonephritis (UTI). *Clinical Infectious Diseases*. 2011;52(5):e103-e120.
3. Clinical Practice Guideline for the management of Asymptomatic Bacteriuria: 2019 Update by the Infectious Diseases Society of America. *Clinical Infectious Diseases*. 2019;68(10):e83-75.
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*. 2018 Dec 21;63(1):e02165-18.