

Once-daily intramuscular amikacin for outpatient treatment of lower urinary tract infections caused by extended-spectrum β -lactamase-producing *Escherichia coli* in children

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Background: The rise in community-acquired urinary tract infections (UTIs) with extended-spectrum β -lactamase (ESBL)-producing *Escherichia coli* strains raises the question of how to treat these infections effectively in pediatric outpatients. Amikacin has shown promising in vitro activity against ESBL-producing urinary isolates of *E. coli*; however, clinical data are limited.

Objective: To investigate the clinical and microbiological outcomes of community-acquired lower UTIs caused by ESBL-producing *E. coli* treated with outpatient amikacin in children.

Materials and methods: A retrospective cohort study was performed on pediatric patients aged ≥ 2 to 18 years treated as outpatients with intramuscular amikacin (given at a dose of 15 mg/kg/day once daily) for community-acquired lower UTIs caused by ESBL-producing *E. coli*, between January 2015 and December 2016.

Results: A total of 53 pediatric patients (38 females) were enrolled in this study. The median age was 4.7 years (range 3–12 years). All *E. coli* isolates were susceptible to amikacin with minimum inhibitory concentrations of ≤ 4 mg/L. The median duration of amikacin treatment was 6 days (range 3–7 days). Favorable clinical and bacteriological responses were observed in 51 of 53 (96%) patients. Development of resistance during treatment with amikacin was seen in only 1 patient (2%), who failed to respond to amikacin treatment and developed acute pyelonephritis with bacteremia. Relapsed lower UTI after initial treatment response occurred in 1 patient (2%) 2 weeks after completion of amikacin treatment. All patients had normal serum creatinine values at baseline, and no significant nephrotoxicity or ototoxicity was observed in any of the patients.

Conclusion: Our study suggests that once-daily intramuscular amikacin could be an alternative option for outpatient treatment of community-acquired lower UTIs caused by amikacin-susceptible ESBL-producing *E. coli* in pediatric patients with normal renal function, when there are no suitable oral antibiotics.

Keywords: amikacin, children, community-acquired urinary tract infections, *Escherichia coli*, extended-spectrum β -lactamase, outpatient

Introduction

The rise in community-acquired urinary tract infections (UTIs) with extended-spectrum β -lactamase (ESBL)-producing *Escherichia coli* strains is becoming a therapeutic challenge in children since there are limited treatment options, especially in outpatient settings.^{1–5} ESBLs are enzymes that confer resistance to most β -lactam antibiotics, including penicillins, cephalosporins, and aztreonam. Infections with ESBL-producing organisms have been associated with poor outcomes, and the carbapenems are regarded

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as the drugs of choice for the treatment of severe infections caused by such organisms.⁶ However, the increase in their use for less severe situations promoted the emergence and spread of resistant strains, especially carbapenemase-producing Enterobacteriaceae, resistant to most available antimicrobials.⁷ Therefore, it has become imperative to investigate alternative carbapenem-sparing agents for treatment of UTIs caused by ESBL-producing *E. coli*.

Aminoglycosides can provide excellent coverage for UTI, and meta-analysis of available randomized evidence recommends adoption of a once-daily dosing in children for potential outpatient treatment.⁸ Low resistance to amikacin in urinary isolates of ESBL-producing *E. coli* is described worldwide both in children and adults.^{2,9} However, there is limited clinical evidence supporting the use of amikacin for the treatment of UTIs caused by ESBL-producing bacteria in children. In this era of increasing antibiotic resistance, we therefore aimed to investigate the clinical and microbiological outcomes of community-acquired lower UTIs due to ESBL-producing *E. coli* treated with outpatient amikacin in children.

Material and methods

Study design and patients

This retrospective study was conducted between January 2015 and December 2016 in the pediatric infectious diseases outpatient clinic of Erzurum Research and Training Hospital, a tertiary-care hospital in Turkey. Pediatric patients treated with outpatient amikacin for community-acquired lower UTIs due to ESBL-producing *E. coli* were screened for study enrollment. Inclusion criteria were: 1) age ≥ 2 to 18 years, 2) presence of at least one of the typical lower UTI symptoms such as dysuria, frequency, urgency, new onset incontinence, hematuria, abdominal or suprapubic pain, 3) pyuria (≥ 10 white blood cells/high power field), 4) positive urine dipstick for nitrites and/or leukocyte esterase, 5) positive monomicrobial urine culture ($\geq 100,000$ colony-forming units [CFU]/mL for midstream urine, and $\geq 50,000$ CFU/mL for catheter urine) for ESBL-producing *E. coli*, which was susceptible to amikacin but resistant to available oral antibiotics, 6) outpatient treatment with amikacin monotherapy at least 3 days.

Amikacin was given intramuscularly at a dose of 15 mg/kg once daily, as recommended by the American Academy of Pediatrics.¹⁰ Urine specimens were obtained by transurethral bladder catheterization in children who were not toilet-trained and by midstream clean-catch method in toilet-trained children. Bag urine samples were not used for urinalysis and urine culture.

Community-acquired UTI was defined as a UTI episode in which, at the time the index urine sample was submitted, the patient was not hospitalized and had not been previously hospitalized during the preceding 30 days. The exclusion criteria were as follows: 1) positive urine culture ≥ 72 h after hospital admission or hospital stay within the preceding month, 2) asymptomatic bacteriuria (defined as a positive urine culture without any clinical manifestations of infection), 3) acute pyelonephritis (defined as having fever with body temperature $\geq 38^\circ\text{C}$ and abdominal or flank pain in older children, and nonspecific signs such as irritability and vomiting in younger children), 4) complicated UTI (defined as an infection in the urinary tract with functional or structural abnormalities such as acute or chronic renal insufficiency, nephrolithiasis, vesicoureteral reflux, neurogenic bladder, and use of permanent urinary catheters or intermittent catheterization), 5) history of hypersensitivity or serious toxic reactions to aminoglycosides, 6) pre-existing renal insufficiency, 7) pre-existing hearing or vestibular dysfunction, 8) treatment with an empiric antimicrobial agent active against ESBL-producing *E. coli* or one that provides clinical improvement in UTI symptoms despite in vitro resistance, 9) patients with insufficient follow-up data.

Data collection

The following data were extracted from the patient's electronic medical records, and Microbiology Laboratory database: baseline patient demographics (age, gender), presence and duration of signs and symptoms of UTI at admission, previous history of UTI, healthcare exposures or hospital stay within 3 months, previous antibiotic use within 3 months, use of empiric antibiotic therapy, use of antimicrobial prophylaxis, initial and control urinalysis, urine cultures and antimicrobial susceptibility test results, baseline renal function tests (serum creatinine, blood urea nitrogen) that were obtained before the initiation of amikacin treatment, follow-up serum creatinine levels, the duration of amikacin treatment, clinical and microbiological response to amikacin treatment, treatment-related adverse effects, and UTI-related hospital re-admission within 30 days after completion of amikacin treatment.

Microbiological methods

The urine samples were plated on Blood Agar and Eosin-Methylene Blue Agar (Biomérieux, Marcy l'Etoile, France) by the semi-quantitative plating method using the calibrated loop technique (0.001 mL). Inoculated plates were incubated aerobically at 37°C for 18 to 24 h. Identification and susceptibility

testing of bacteria was performed by using the BD Phoenix automated microbiology system (Becton Dickinson Diagnostic Systems, Sparks, MD, USA) according to the manufacturer's instructions. Antimicrobial susceptibilities and ESBL production were determined according to the European Committee on Antimicrobial Susceptibility Testing guidelines.¹¹ The Minimal Inhibitory Concentration (MIC) susceptibility breakpoints used for the antibiotics tested were as follows: ampicillin ≤ 8 mg/L, amoxicillin–clavulanate $\leq 8/2$ mg/L, ceftriaxone ≤ 1 mg/L, cefuroxime ≤ 8 mg/L, ceftazidime ≤ 1 mg/L, cefepime ≤ 1 mg/L, aztreonam ≤ 1 mg/L, ciprofloxacin ≤ 0.5 mg/L, amikacin ≤ 8 mg/L, gentamicin ≤ 2 mg/L, netilmicin ≤ 2 mg/L, ertapenem ≤ 0.5 mg/L, imipenem ≤ 2 mg/L, meropenem ≤ 2 mg/L, piperacillin ≤ 8 mg/L, piperacillin–tazobactam $\leq 8/4$ mg/L, trimethoprim-sulfamethoxazole (TMP-SMX) $\leq 2/38$ mg/L, colistin ≤ 2 mg/L, tigecycline ≤ 1 mg/L. These methods and the breakpoints for susceptibility remained unchanged during the study period.

Outcomes

The primary outcomes of the study were clinical and microbiological outcomes of UTIs. As secondary outcome, we evaluated the development of nephrotoxicity and ototoxicity associated with amikacin. Follow-up medical records of patients were reviewed to assess the efficacy (based on clinical and microbiological outcomes) and adverse events (nephrotoxicity and ototoxicity) of amikacin treatment. All of the efficacy and toxicity outcomes were evaluated at outpatient clinic visits on the third day of and at the end of the treatment. Control urine cultures were obtained on the third day of the amikacin treatment. At the visits, the patients were encouraged to return whenever symptoms occur that could be related to UTI.

Clinical outcome was classified as favorable clinical response (resolution of presenting symptoms of UTI without requirement of any additional antibiotics at the end of the amikacin treatment) and poor clinical response (persistence or progression of presenting symptoms of UTI during amikacin treatment). Microbiological outcome was classified as favorable bacteriological response (eradication of the causative microorganism in the control urine culture) and poor bacteriological response (persistence of the causative microorganism on control urine culture). Relapse was defined as the development of a UTI with ESBL-producing *E. coli* within 30 days after completion of amikacin treatment.

Because of the potential nephrotoxicity associated with aminoglycosides use, renal function as determined by serum creatinine levels was measured before the administration of amikacin and at the end of treatment, as recommended

in the product information¹² and by the Infectious Diseases Society of America (IDSA) guidelines.¹³ Nephrotoxicity was defined as doubling of baseline serum creatinine compared with treatment initiation and/or elevation of serum creatinine values beyond the estimated normal range for the patient's age group.^{14,15} Ototoxicity was defined as any symptoms or signs of the following after amikacin use: nausea, vomiting, nystagmus, ataxia, dizziness, vertigo, tinnitus or hearing loss.¹⁶ Monitoring of ototoxicity was made by the subjective patient assessment at outpatient clinic visits.

Ethics statement

The Ethical Committee of Erzurum Research and Training Hospital approved this study (approval number: 2017/04-31) with a waiver of informed consent for retrospective data collection under the condition of anonymously stored data collected.

Statistical analysis

Data were analyzed by frequency and percentage for qualitative variables, and mean \pm SD, median, minimum, and maximum values for quantitative variables.

A paired *t*-test was carried out to assess whether there was a significant difference between the mean serum creatinine values that were obtained before and after the administration of amikacin. Statistical analyses were performed using SPSS 21 (IBM SPSS Inc, Chicago, IL, USA) and the significance was set at $p < 0.05$.

Results

A total of 53 eligible patients (38 females) were enrolled in this study. The median age of the patients was 4.7 years (range 3–12 years). Of the 53 patients, 16 (30%) had a previous history of culture-positive UTI. Most of the patients ($n=48$, 90%) had received antibiotics in the last 3 months, including second- and third-generation cephalosporins ($n=18$), amoxicillin–clavulanate ($n=17$), and TMP-SMX ($n=13$), for either presumptive diagnosis of UTI without prior urine studies or treatment of other infections. Prophylactic antibiotic use was recorded in 16 of 53 (30%) patients for recurrent UTI: TMP-SMX in 8 patients, nitrofurantoin in 5 patients, and cephalexin in 3 patients. According to in vitro susceptibility test results, 18 of 53 (34%) patients received inappropriate empiric therapy that did not provide clinical improvement, including oral formulations of third-generation cephalosporin ($n=11$), amoxicillin–clavulanate ($n=4$), and TMP-SMX ($n=3$). The remaining 35 (66%) patients who did not receive empiric antimicrobial therapy, were initially

seen in other outpatient clinics and consulted us with positive urine culture results for antibiotic treatment recommendation.

Amikacin was initiated as definitive treatment (after urine culture susceptibility results were made available) in all of the patients. All *E. coli* isolates were susceptible to amikacin with MICs of ≤ 4 mg/L but resistant to amoxicillin–clavulanate (MICs $>32/2$ mg/L) and TMP-SMX (MICs $>4/76$ mg/L) (Figure 1). The median duration of amikacin treatment was 6 days (range 3–7 days). Treatment outcomes and adverse events of amikacin treatment are summarized in Table 1. Poor clinical and bacteriological responses were seen in only 1 patient who subsequently developed acute pyelonephritis and was hospitalized 3 days after the initiation of amikacin. Treatment was changed to intravenous ertapenem (15 mg/kg/dose twice daily). On hospital day 3, ESBL-producing *E. coli* that was resistant to amikacin (MIC >16 mg/L) but susceptible to ertapenem (MIC ≤ 0.25 mg/L) was isolated from urine and blood cultures. The patient was discharged in good condition on hospital day 10. No treatment changes were required for resolution of symptoms in all other patients. Relapsed lower UTI after initial treatment response was seen in another 12-year-old female patient 2 weeks after treatment completion. ESBL-producing *E. coli* susceptible to both amikacin (MIC ≤ 4 mg/L) and nitrofurantoin (MIC ≤ 16 mg/L) was isolated again from urine culture, and the patient was successfully treated with a 7-day course of nitrofurantoin (7 mg/kg/day orally in 4 divided doses). In this patient, we could not find any underlying functional or anatomic urinary tract abnormalities for the development of relapsed UTI, except for bladder and bowel dysfunction.

There was no significant nephrotoxicity in any of the patients. All patients had normal serum creatinine values at baseline (median 0.4 mg/dL, range: 0.2–0.5 mg/dL), and differences between the mean serum creatinine levels before the initiation and at the end of amikacin treatment were not statistically significant (0.45 ± 0.11 mg/dL vs 0.47 ± 0.13 mg/dL, $p=0.24$). There were no subjective changes in hearing, tinnitus, and clinically apparent vestibular dysfunction in any of the patients.

Discussion

Given the limited treatment options available outside the hospital setting, management of UTI due to ESBL-producing *E. coli* is challenging in children. When choosing a treatment regimen, physicians should consider such factors as the local susceptibility pattern, adverse effects, cost effectiveness, and selection of resistant strains.^{4,5} In recent years, aminoglycosides are undergoing a resurgence in use because of widespread resistance to other therapeutic classes.¹⁷ The results of the Study for Monitoring Antimicrobial Resistance Trends surveillance studies from different parts of the world indicate

Table 1 Treatment outcomes and adverse events of outpatient amikacin therapy (n=53)

Outcome	n (%)
Clinical and microbiological outcomes	
Favorable clinical and bacteriological responses	51 (96)
Poor clinical and bacteriological responses	1 (2)
Relapse	1 (2)
Adverse events	
Nephrotoxicity	0 (0)
Ototoxicity	0 (0)

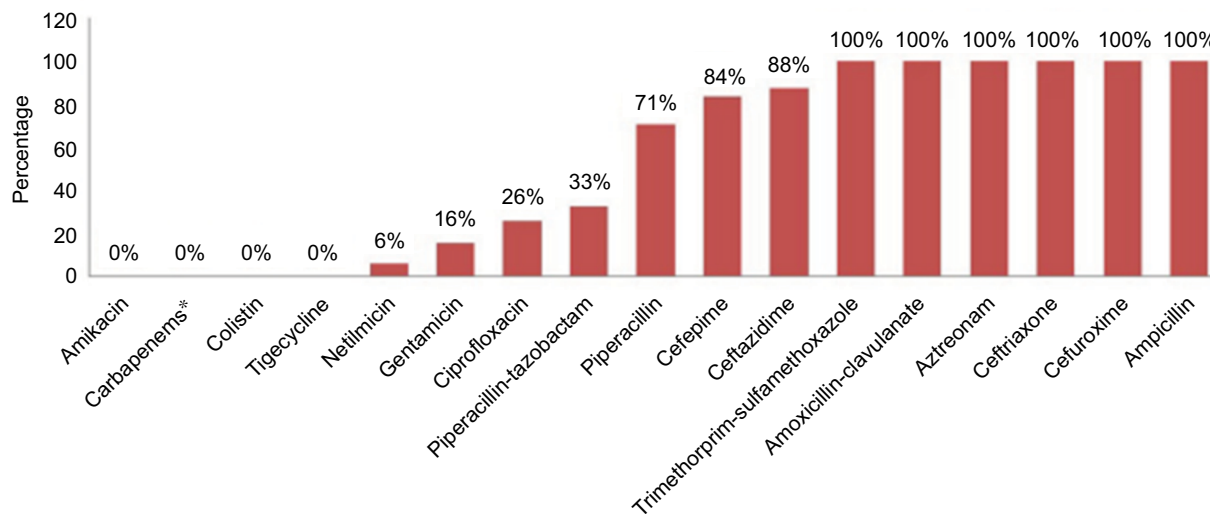


Figure 1 The antimicrobial resistance profiles of extended-spectrum β -lactamase-producing *Escherichia coli* isolates (n=53). Note: *Carbapenems: meropenem, imipenem and ertapenem included.

that amikacin maintains a high level of in vitro activity against ESBL-producing strains.^{9,18} However, clinical data for the use of amikacin for the treatment of UTIs due to ESBL-producing *E. coli* are limited in children. Only 2 adult studies have reported the use of amikacin for outpatient treatment of UTIs caused by ESBL-producing strains.^{19,20} To the best of our knowledge, this is the largest and the first pediatric cohort to date that examines the clinical and microbiological outcomes of community-acquired lower UTIs due to ESBL-producing *E. coli* treated with outpatient amikacin.

Our study suggests that once-daily intramuscular amikacin could be an alternative option for outpatient treatment of children with community-acquired lower UTIs caused by amikacin-susceptible ESBL-producing *E. coli* strains. These findings are in agreement with those of previous adult studies.^{19,20} Park et al²¹ reported on the clinical and microbiological effects of aminoglycosides in adults and children with UTIs caused by ESBL-producing strains, and the efficacy of aminoglycoside combination therapy has also been demonstrated in children with febrile UTIs due to ESBL-producing strains.²²

Based on identification and susceptibility results, alternatives to carbapenems should be used to treat uncomplicated UTIs caused by ESBL-producing organisms. The antimicrobial agents most commonly used to treat uncomplicated UTIs include the β -lactams, TMP-SMX, fluoroquinolones, fosfomycin, and nitrofurantoin.^{4,5} However, ESBL-producing *E. coli* strains are frequently resistant to commonly prescribed oral antibiotics such as TMP-SMX, penicillins, and cephalosporins.²³ This condition poses significant therapeutic challenges in children, in whom fewer antibiotics are approved for clinical use.⁵ The high rates of TMP-SMX and amoxicillin-clavulanate resistance observed in our study are thought to be related to the excessive usage of these 2 antibiotics for the prophylaxis or treatment of UTIs and other common pediatric infections. Additionally, all of the patients in our study were aged ≤ 12 years, which limits the use of fluoroquinolones and fosfomycin. Fluoroquinolones are not recommended for routine use in children < 18 years of age because of the osteoarticular side effects observed in juvenile animals. Indications for fluoroquinolone use in patients < 18 years, as stated by the US Food and Drug Administration, include treatment of complicated UTIs and pyelonephritis due to *E. coli*.²⁴ Fosfomycin is an oral antimicrobial agent that has broad activity against multi-drug resistant pathogens, including ESBL-producing *E. coli*.²⁵ However, pediatric experience with fosfomycin is limited, since its safety and effectiveness in children aged ≤ 12 years have not been

established.²⁶ Nitrofurantoin is another potential treatment option for lower UTI caused by ESBL-producing *E. coli*, if the isolate is known to be susceptible.^{4,5} However, during the study period, the susceptibility testings for nitrofurantoin and fosfomycin were not routinely performed by our microbiology laboratory, unless requested by the treating physician. Therefore, as in our patients, amikacin could be an alternative option for the outpatient treatment of lower UTIs caused by ESBL-producing *E. coli*, if there is no suitable oral antibiotic therapy. To prevent the development of resistance, carbapenems should only be used in patients with severe infections with ESBL-producing Enterobacteriaceae other than UTIs.

Amikacin monotherapy seems to be a useful alternative for the outpatient treatment of children with uncomplicated ESBL UTIs because of its high urinary excretion (aminoglycosides reach concentrations in the urine 25–100-fold that of serum), low resistance rates, easy intramuscular administration, and low cost.^{5,8,16} Certain pharmacodynamic and kinetic properties of the aminoglycosides are important for their clinical application.²⁷ Aminoglycosides demonstrate both concentration-dependent killing and post-antibiotic effect that allow a once-daily administration schedule. A once-daily schedule produces longer post-antibiotic effect, significantly higher peak concentration and greater bactericidal activity. Compared with multiple-daily dosing, once-daily dosing causes similar or lower rates of nephrotoxicity.^{8,16}

The main concerns with the use of aminoglycoside antibiotics are nephrotoxicity and ototoxicity. The risk of nephro- and ototoxicity is greater in patients with impaired renal function, and in patients with normal renal function treated at higher doses and/or for periods longer than those recommended.^{12,27} Aminoglycoside-induced ototoxicity may result in either vestibular or cochlear damage. Cochlear damage is manifested as tinnitus or high frequency hearing loss, whereas vestibular damage is associated with vertigo, nausea, vomiting, nystagmus, and ataxia.¹⁶ Monitoring for ototoxicity involves subjective patient assessment for the presence of hearing and vestibular dysfunction.¹³ The use of objective testing such as audiometry is generally reserved for patients who have subjective symptoms, pre-existing hearing dysfunction, and for those scheduled to receive prolonged therapy.^{12,13} In this study, although we did not routinely perform pre- and post-treatment audiometry, clinically detectable ototoxicity was not observed. There were no significant changes in serum creatinine levels. To prevent the development of nephro- and ototoxicity, we administered amikacin at the recommended dose^{10,12} and duration^{12,27} in patients with normal renal function. Current recommendations for

once-daily dosing of all aminoglycosides are for only up to 5–6 days.²⁷ In the present study, amikacin was given in a total daily dose of 15 mg/kg and the treatment duration was median 6 days, and did not exceed 7 days. The duration of antibiotic treatment for afebrile children with presumed lower UTI has been controversial; however, 3 days of TMP-SMX or 5 days of other antibiotics is thought to be effective.⁴ In our clinic, we usually treat children aged ≥ 2 years with uncomplicated lower UTI for at least 5 days.

In our outpatient clinic, there is only 1 follow-up visit for children with uncomplicated lower UTI and we do not routinely perform control urine culture if the patient responds well to antibiotic therapy. However, in the present study, control urine cultures were obtained in all children to ensure the bacteriological efficacy of amikacin against ESBL-producing *E. coli* isolates. In patients receiving aminoglycoside therapy, clinical monitoring for vestibular and hearing dysfunction at each visit and monitoring of serum creatinine levels at least twice a week are recommended by guidelines issued by the IDSA for the treatment of outpatient parenteral antimicrobial therapy (OPAT).¹³ It was also recommended that patients should be seen after completion of OPAT to be sure they have responded to therapy, are doing well and have had no adverse events.¹³ We therefore arranged the follow-up visits on the third day of and at the end of the treatment to monitor the efficacy and toxicity outcomes.

Although the prevalence of aminoglycoside resistance has remained relatively low compared with that for cephalosporins or fluoroquinolones, some investigators reported increased amikacin resistance following unrestricted use of this antibiotic.²⁸ One review of a large number of clinical trials found that development of resistance in Gram-negative bacteria during treatment with aminoglycosides resulted in treatment failure in 85% of the cases,²⁹ as in our 1 case who failed to respond to amikacin treatment due to development of resistance. The judicious use of existing antimicrobials to preserve their future effectiveness and the future development of novel agents effective against ESBL-producing strains in children will help expand the therapeutic repertoire available to pediatricians to treat resistant Gram-negative infections.

This study has the following limitations. First, this is single-center, retrospective study with a relatively small number of patients, and thus, cannot allow generalization of clinical and microbiological outcomes and adverse events. Second, ototoxicity was estimated only subjectively and routine audiometry was not performed. Third, there was no control group to compare the efficacy of amikacin versus other antimicrobials.

Despite these limitations, this is the first pediatric study that gives important data on whether the use of amikacin could be an alternative option for outpatient treatment of lower UTIs caused by ESBL-producing *E. coli* in areas where antibiotic resistance rate of the urinary pathogens is high.

Conclusion

The results of our study suggest that pediatric patients with community-acquired lower UTIs caused by amikacin-susceptible ESBL-producing *E. coli*, with no suitable oral antibiotic therapy, can be treated as outpatients with once-daily intramuscular amikacin, if patients are closely monitored for renal function and ototoxicity. Further randomized controlled studies, including a large number of cases are needed to exactly define the effectiveness and safety of once-daily dosing of amikacin in pediatric patients with UTIs due to ESBL-producing *E. coli*.

Author contributions

All authors contributed toward data analysis, drafting and critically revising the paper and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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