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Original article

Resistance and efficiency of amikacin in critically ill septic children: a cross-sectional study

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Abstract

Background: Therapeutic drug monitoring facilitates the individualization of amikacin dosing for patients based on pharmacodynamics and pharmacokinetics. Its efficacy is measured by peak serum concentration (C_{peak}) / minimum inhibitory concentration (MIC) ratio. This study aims to determine the efficacy of 15 mg/kg/day of amikacin in critically ill septic pediatric patients.

Methods: This cross-sectional analytic study involved 25 pediatric critically ill septic patients. All patients received amikacin based on clinical diagnosis and/or culture results. Amikacin C_{peak} and MIC were measured.

Results: Amikacin C_{peak} was not achieved in 44% of the study group, with the MIC being at least 64 mcg/mL, leading to a very low C_{peak}/MIC ratio.

Conclusion: Critically ill pediatric patients who are administered amikacin require frequent monitoring and dose adjustment to achieve the target level, as subtherapeutic levels may contribute to resistance, while elevated levels are linked to non-oliguric acute kidney injury.

Keywords

Amikacin, critically ill, MIC, sepsis, therapeutic drug monitoring, pediatrics.

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Background

Aminoglycosides represent a class of antibiotics that have been utilized since the 1940s for the treatment of a broad spectrum of bacterial infections. The primary resistance mechanism against these antibiotics involves enzymatic modification by aminoglycoside-modifying enzymes, which are categorized into acetyltransferases, phosphotransferases, and nucleotide transferases. To address this issue, attempts have been made to develop new semisynthetic aminoglycosides since 1970. Amikacin is the most utilized semisynthetic aminoglycoside, demonstrating resistance to most aminoglycoside-modifying enzymes [1]. Appropriate administration is one of the crucial measurements for effective treatment and the prevention of antimicrobial resistance, which has recently become a significant health issue [2]. Previous studies have reported that approximately 30-40% of critically ill patients exhibit aminoglycoside plasma concentrations below the target peak levels when utilizing standard dosing regimens, which may contribute to antibiotic resistance. It is projected that resistant bacteria will result in the death of 10 million of the population by 2050 [3]. Amikacin efficacy in sepsis is affected by the development of resistance as well as changes in hemodynamics and pharmacodynamics due to critical illness. In the Intensive Care Unit (ICU), antibiotic concentrations exceed the therapeutic window in up to 41% of adult patients [4] and 95% in critically ill pediatrics [5]. This may be attributed to amikacin's narrow range for achieving an effective dose along with minimizing adverse side effects [6]. Prior studies indicated that optimal measured peak and trough concentrations with once-daily dosing averaged 40-45 mcg/mL and 1-2 mcg/mL, respectively [7, 8]. Therefore, therapeutic drug monitoring (TDM) is recommended for critically ill patients to evaluate the efficacy and determine the appropriate redosing [9]. Furthermore, an optimal amikacin efficacy is indicated by a peak serum concentration (C_{peak}) to the infective bacteria's minimum inhibitory concentration (MIC) ratio exceeding 8-10, serving as a predictor for therapeutic potency [10]. Moreover, there is a limited number of studies examining the efficacy and resistance to amikacin in pediatric patients across various geographic regions. This study aims to evaluate the peak amikacin levels in critically ill pediatric patients and the potential degree of resistance.

Patients and methods

A cross-sectional study was conducted over a 6-month period (from June to December 2020) in the Pediatric ICUs (PICU) and at a tertiary hospital. The study included 25 patients aged between 1 month and 12 years of critically ill patients (septic shock). Critically ill patients with unstable hemodynamics and organ failure due to infection were classified as having a severe life-threatening infection (septic shock). This classification was reassessed using the PRISM III score, which serves as an indicator of illness severity [11]. As well, the patients were included in our study if they fulfilled any of the following definitions for pediatric sepsis based on the 2005 International Pediatric Sepsis Consensus Conference [12]: 1) sepsis (systemic inflammatory response syndrome [SIRS] and suspected or confirmed infection); 2) severe sepsis (sepsis and cardiovascular dysfunction, respiratory dysfunction, or ≥ 2 non-cardiorespiratory organ system dysfunctions); 3) septic shock (sepsis and cardiovascular dysfunction are defined as either hypotension, need for vasoactive drugs, or impaired perfusion despite fluid resuscitation). Seven patients on renal replacement therapy with pre-existing renal dysfunction or known chronic renal disease were excluded from the study as any patient with renal dysfunction or fluid imbalance was excluded initially from our study according to our exclusion criteria. Peripheral blood samples of 3-5 mL for C_{peak} determination were collected 30 minutes after the complete infusion of the third amikacin once-daily dose (15 mg/kg/dose), as once-daily administration of aminoglycosides in adults and children is better tolerated than traditional dosing schedules (2 or 3 times daily), and it offers potential pharmacodynamic advantages [13]. Other

blood tests were conducted on the day amikacin administration commenced and on the day of serum amikacin drug monitoring, including complete blood count, creatinine, and C-reactive protein (CRP). Clinical data comprised PRISM III scores, temperature, urine output (UOP), and fluid balance recorded on the initial day of amikacin therapy and on the day of amikacin level determination (third dose). Blood cultures were obtained from all patients, and MIC determination was performed on positive cultures using Biomérieux™ Amikacin Etest®. The ratio of C_{peak} to MIC was subsequently calculated. Comparable procedures were implemented for the peak amikacin level following the third dose (subtherapeutic level [C_{peak} < 20 mcg/mL], therapeutic level [C_{peak} ≥ 20 and ≤ 40 mcg/mL] and toxic level [C_{peak} > 40 mcg/mL]). Resistance to amikacin therapy was considered when MIC breakpoint > 64 mcg/mL according to the Clinical and Laboratory Standards Institute (CLSI)'s *Performance Standards* published in 2022 [14]. Blood samples were dispatched to the drug laboratory within 2 hours of collection and were stored at -20°C in the laboratory. The Emit® Amikacin Assay was used to determine amikacin medication concentrations (Siemens, Frimley, Camberley, UK). The Emit® Amikacin Assay is a homogeneous enzyme immunoassay designed for the quantitative measurement of amikacin in human serum or plasma. The Research Ethics Committee of Kasr Al Ainy Faculty of Medicine, Cairo University, reviewed and approved the study protocol (N:ms-129-2020). Informed written consent was obtained from all enrolled patients' parents and/or guardians.

Statistical analysis

Statistical analysis was conducted using IBM® SPSS® software version 20.0 (IBM Corporation, Armonk, NY). Numbers and percentages were used to describe qualitative data. The Kolmogorov-Smirnov test was utilized to verify the Gaussian distribution. Quantitative data were characterized using range (minimum and maximum), median and standard deviation. The significance of the obtained results was evaluated at the 5% level. The tests employed were: 1) Chi-square test (to compare various groups using category variables); 2) Mann Whitney test (to compare two independent groups with non-normally distributed quantitative variables); 3) Kruskal Wallis test (for non-parametric comparisons of more than two independent groups with non-normally distributed data, followed by Dunn's *post hoc* test for pairwise comparisons); 4) Wilcoxon signed ranks test (to compare paired or related samples with non-normally distributed data); 5) correlation (to assess monotonic associations between two continuous variables, with ϱ ranging from −1.0 [perfect inverse] to +1.0 [perfect direct]).

Results

This study was conducted in ICUs at Cairo University Children's Hospital. Twenty-five patients met the inclusion criteria of this study and were treated with amikacin. **Tab. 1** presents the demographic data and diagnoses in the studied group. Pneumonia requiring hospital admission was the most common cause of hospitalization, followed by septic shock with bloodstream infections. Blood cultures were collected from all 25 patients, as summarized in **Tab. 1**. 56% of patients showed organism growth, while 44% had no growth. **Tab. 2** presents clinical and laboratory data of the studied patients including the commencement of amikacin therapy and the day of TDM. **Tab. 3** shows amikacin drug level,

Table 1. Demographics and diagnoses of the study group (n = 25).

		Values
Age (months), median (range)		36 (2-144)
Male:female		13:12
Cause of hospitalization	**Pneumonia**	14 (56%)
	Septic shock	4 (16%)
	CNS infection	1 (4%)
	Guillain-Barré sepsis	1 (4%)
	Post-operative (intestinal perforation)	1 (4%)
	Gastroenteritis	1 (4%)
	Urinary tract infection	1 (4%)
	Cellulitis	1 (4%)
	Sepsis of unknown origin	1 (4%)
Organism growth	**No growth**	11 (44%)
	Klebsiella pneumonia	9 (36%)
	Pseudomonas aeruginosa	5 (20%)
	Escherichia coli	0 (0%)
	Neisseria meningitides	0 (0%)

Values are expressed as n (%) unless otherwise specified.
CNS: central nervous system.

Table 2. Clinical and laboratory data distribution among the study group (n = 25).

	Values
PRISM III score	49 (19-67)
Urine output (mL/kg/hour) at the first dose of amikacin	2.1 (1.1-5.8)
Urine output (mL/kg/hour) at the time of TDM	2.1 (1.2-5.7)
Fluid balance (mL) at the first dose of amikacin	215 (10-868)
Fluid balance (mL) on the day of TDM	140 (20-996)
WBCs (per µL of blood) at the first dose of amikacin	19 (11.2-43.3)
WBCs (per µL of blood) at the time of TDM	14 (7-12.8)
Hb (g/dL) at the first dose of amikacin	10.7 (7-12.8)
Hb (g/dL) on the day of TDM	10 (7.5-12.4)
Platelets (per µL of blood) at the first dose of amikacin	443 (89-1,101)
Platelets (per µL of blood) on the day of TDM	405 (100-1,090)
BUN (mg/dL) at the first dose of amikacin	13 (7-47)
BUN (mg/dL) at the time of TDM	13 (7-42.9)
Creatinine (mg/dL) at the first dose of amikacin	0.6 (0.4-1.1)
Creatinine (mg/dL) at the time of TDM	0.6 (0.2-1)
CRP (mg/dL) at the first dose of amikacin	56 (11.9-343)
CRP (mg/dL) at the time of TDM	40.7 (6-242)

Values are expressed as median (range).
BUN: blood urea nitrogen; CRP: C-reactive protein; Hb: hemoglobin; TDM: therapeutic drug monitoring; WBCs: white blood cells.

MIC, C_{peak}/MIC ratio, and the distribution of C_{peak} among the study group, where amikacin was subtherapeutic in 44% cases, whereas it was toxic in 16%. MIC was at least 64 mcg/mL, resulting in a very low C_{peak}/MIC ratio. **Tab. 4** reveals the clinical and laboratory variables according to different amikacin levels: subtherapeutic level (C_{peak} < 20 mcg/mL), therapeutic level (C_{peak} ≥ 20 and ≤ 40 mcg/mL) and toxic level (C_{peak} > 40 mcg/mL). Toxic amikacin levels were associated with a mean positive fluid balance approximately twice that observed in the therapeutic group, as depicted in **Tab. 4**.

Table 3. Amikacin drug level, MIC, C_{peak}/MIC ratio, and distribution among the study group (n = 25).

	Values
TDM (mcg/mL), median (minimum-maximum)	20.1 (2.5-50)
MIC (mcg/mL), median	> 64
C_{peak}/MIC ratio, median (minimum-maximum)	0.12 (0.009-0.2)
C_{peak} < 20 mcg/mL, n (%)	11 (44%)
C_{peak} ≥ 20 and ≤ 40 mcg/mL, n (%)	10 (40%)
C_{peak} > 40 mcg/mL, n (%)	4 (16%)

C_{peak}: peak serum concentration; MIC: minimum inhibitory concentration; TDM: therapeutic drug monitoring.

Table 4. Clinical and laboratory variables according to amikacin level (n = 25).

	Subtherapeutic level (C_{peak} < 20 mcg/mL)		Therapeutic level (C_{peak} ≥ 20 and ≤ 40 mcg/mL)		Toxic level (C_{peak} > 40 mcg/mL)		p-value
	Mean	SD	Mean	SD	Mean	SD	
Age (months)	35	32.4	32	40.8	90.5	64.5	0.062
Weight (kg)	11.91	7.7	15	17.3	28.5	19.7	0.157
Temperature (Celsius)	38.49	38.3	38.8	0.56	38.5	0.35	0.12
PRISM III score	43.09	49	48.1	17.7	39.75	22	0.32
Urine output (mL/kg/hour) at the beginning of therapy	2.79	2.1	2.49	1.25	2.1	0.62	0.12
Urine output (mL/kg/hour) on the day of TDM	2.7	2.1	2.56	1.16	2.8	1.52	0.2
Fluid balance (mL) at the beginning of therapy	+253	146	+218	166	+403	167	0.11
Fluid balance (mL) on the day of TDM	+266	140	+167	165	+407	400	**0.03**
WBCs (per µL of blood) at the beginning of therapy	19.73	6.08	15.3	5.34	28.33	11.6	**0.014**
WBCs (per µL of blood) on the day of TDM	17.07	7.99	12.7	3.48	21.75	6.13	0.059
Hb (g/dL) at the beginning of therapy	10.05	1.96	11.6	1.79	7.58	0.4	**0.002**
Hb (g/dL) on the day of TDM	10.01	1.48	11	1.93	9.33	1.01	0.182
Platelets (per µL of blood) at the beginning of therapy	452.45	257	432	176	545.5	281	0.709
Platelets (per µL of blood) on the day of TDM	409.73	258.9	381	157	451	262	0.868
BUN (mg/dL) at the beginning of therapy	20	12.33	16.4	13.7	15.93	6.46	0.754

BUN: blood urea nitrogen; Hb: hemoglobin; TDM: therapeutic drug monitoring; WBCs: white blood cells.

Discussion

Amikacin, a narrow therapeutic index drug, is broadly used in the pediatric population for various diseases [15]. In critically ill patients, the timely determination of an appropriate initial dose of amikacin is essential [16]. The efficacy and safety of aminoglycoside therapy require the maintenance of acceptable serum concentrations through TDM to prevent the emergence of aminoglycoside-resistant organisms [17] due to inappropriate amikacin use and to support antimicrobial stewardship [18]. Pharmacokinetic parameters of amikacin, along with factors such as weight, sex, and renal function, contribute to inter-individual variability. In this study, we studied the amikacin efficacy in our Egyptian pediatric patients as it has not been thoroughly investigated. A once-daily dose of amikacin was administered at 15 mg/kg/day, as previously demonstrated to be better tolerated than traditional dosing schedules [13, 19]. Furthermore, once-daily dosing is considered safe and exhibits reduced toxicity [15, 20]. Additionally, amikacin possesses a post-antibiotic effect [2], where there is residual bactericidal activity that is sustained for a time after drug administration.

The most common isolated organism in our study was *Klebsiella pneumonia* (9 cases, 36%), followed by *Pseudomonas aeruginosa* (5 cases, 20%). This concurs with a study by Yusuf and Chowdhury [21], where Gram-negative bacilli were the most common isolated organisms. Conversely, research conducted in Europe indicated that Gram-positive bacteria were the predominant organisms, whereas studies from the USA found that viruses were the most common pathogens [22]. The distribution of Gram-positive and Gram-negative bacteria was equal in Brazil, with *Staphylococcus aureus* identified as the most frequently isolated organism [23]. However, no growth was found in 11 cases (44%), which is higher than the percentage found in the study by Roger et al. [3].

Our study demonstrated that peak concentration of amikacin level was in the therapeutic range only in 40% of the studied group. A study conducted in Iran found that 38% of the peak levels fell within the therapeutic range [24]. Critically ill patients may necessitate higher doses of amikacin due to an increased volume of distribution, as observed in a study involving critically ill surgical patients who required doses of up to 20 mg/kg to reach the therapeutic target [25]. Sadeghi et al. [26] suggested that administering higher-than-standard doses of amikacin at extended intervals may be more suitable than the standard once-daily dosing for elderly critically ill patients.

Unfortunately, MIC demonstrated a mean > 64 mcg/mL for the positive culture, indicating a significantly elevated MIC level and high prevalence of resistance to amikacin; however, other studies reported MIC values ranging from 0.125 to 32 mcg/mL [27, 28], and although we appreciate that CLSI breakpoints for amikacin has been lowered to > 16 mcg/mL since 2023, which was after our study, our results remains above the updated breakpoints [14, 29]. The World Health Organization (WHO) lists antibiotic resistance as one of today's most significant threats to global health, food security, and development [30]. Unfortunately, our findings contradict the systematic review and meta-analysis conducted by Luo et al. [31], but this could be explained by the high resistance of the organisms to amikacin in our settings. Luo et al.'s study [31] indicates that amikacin exhibited low drug resistance and high drug susceptibility in children with extended-spectrum beta-lactamase-producing *Enterobacterales* (ESBL-PE) infections, suggesting it is a viable treatment option for the treatment of the infection caused by ESBL-PE. Gram-negative resistance continues to be a global concern, with certain countries, as we found in our study, experiencing resistance rates above the average. Multidrug resistance in the Asia-Pacific region has escalated rapidly, with limited new antimicrobials available to address this issue [32].

A study done by Alqahtani et al. [33] recommended a combination of antibiotics therapy when the MIC level ≥ 8 mcg/mL [27]. The C_{peak}/MIC ratio observed in our study was significantly low compared to other research, with a median ratio of 0.12 across the entire study population (0.009-0.2). This contrasts with the expected ratio of ≥ 2, as reported by Alqahtani et al. [33], who demonstrated that a dosage of 15 mg/kg/day resulted in a C_{peak}/MIC ratio of ≥ 2 in over 90% of patients. In contrast, a study by Uc-Cachón et al. [34] revealed that the percentage of amikacin resistance ranged from 9.64% to 58.49% across different microorganisms. This result supports our finding of increasing anti-microbial resistance. A C_{peak}/MIC ratio > 8 is associated with successful clinical outcomes [2], while a C_{min} greater than 10 mcg/mL elevates the risk of toxicity [35]. In our study, the toxic level of amikacin was found to correlate with an increased positive fluid balance, and this may be associated with adverse outcomes,

as a study done by McWilliam et al. [36] reported that 20% of patients experienced acute kidney injury and the primary clinical manifestation was non-oliguric acute kidney injury resulting from reduced glomerular filtration. As well, a study done by De Winter et al. [37] reported that toxic amikacin level does not directly cause fluid overload, and that its renal and systemic effects can worsen or perpetuate positive fluid balance, especially in vulnerable patients, as in septic patients amikacin toxicity may exacerbate endothelial dysfunction, increasing vascular permeability and promoting third-spacing of fluids, further skewing fluid balance.

This study had several limitations, including a small sample size and a single-center design.

Conclusion

Critically ill pediatric patients receiving amikacin need frequent monitoring and dose adjustment to maintain therapeutic levels, as subtherapeutic concentrations may contribute to resistance, while elevated levels are associated with non-oliguric acute kidney injury. Take-home messages are presented in **Tab. 5**.

Table 5. Highlight box.

Amikacin is a narrow therapeutic spectrum drug with challenging pharmacodynamics in critically ill patients, so TDM is warranted for escalating the dose of amikacin toward an effective dose to avert the emergence of drug resistance, which has a remarkable influence on minimum inhibitory concentration and, subsequently, drug efficiency.

TDM: therapeutic drug monitoring.

Availability of data

The data sets generated and analyzed during the current study are available from the corresponding author.

Declaration of interest

The Authors declare that there is no conflict of interest.

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