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Comparative Renal and Auditory Safety of Once-Daily Gentamicin at 5 mg/kg Versus 4 mg/kg in Neonatal Sepsis: A Prospective Cohort Study in Tanzania

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ABSTRACT

Neonatal sepsis remains a major cause of newborn morbidity and mortality in resource-limited settings, where gentamicin is widely used as empirical therapy. In Tanzania, once-daily gentamicin (4–5 mg/kg) is recommended, but the 5 mg/kg regimen is commonly used without routine therapeutic drug monitoring (TDM), raising concerns about nephrotoxicity and ototoxicity. Although the 4 mg/kg once-daily regimen has generally been associated with a lower risk of aminoglycoside-related toxicity than higher-dose regimens, its use in Tanzania remains limited, with the 5 mg/kg regimen more commonly employed. This variation between international evidence and local prescribing practice highlights the importance of evaluating whether the lower-dose regimen may offer a safer therapeutic option for Tanzanian neonates. The growing recognition of medication-related kidney injury in children further highlights the need for safer antimicrobial strategies. However, local evidence comparing the 5 mg/kg and 4 mg/kg regimens remains limited. This study compared the renal and auditory safety of these regimens in term neonates. This prospective observational cohort study included 375 term neonates receiving gentamicin 5 mg/kg (n=125), gentamicin 4 mg/kg (n=125), or ceftriaxone/cefotaxime (n=125). Renal function was assessed using serum creatinine and urinary kidney injury molecule-1 (uKIM-1), while auditory function was evaluated using automated auditory brainstem response (AABR). Nephrotoxicity was defined using kidney disease: Improving Global Outcomes (KDIGO) criteria and ototoxicity as ≥20 dB AABR threshold increase from baseline. Acute kidney injury (AKI) was more frequent and severe in the 5 mg/kg group, with stage I, II, and III AKI occurring in 35.2%, 14.4%, and 1.6%, respectively. The 4 mg/kg group had 2.4% stage I AKI with no stage II/III cases, while no AKI occurred in the comparison group ($p<0.001$). Ototoxicity occurred in 4.0% receiving 5 mg/kg, with no cases in other groups ($p<0.05$). The 5 mg/kg regimen was associated with greater renal and auditory toxicity than 4 mg/kg, supporting lower-dose strategies where TDM is unavailable.

Introduction

Between 1990 and 2021, there has been a significant global reduction in neonatal mortality, decreasing from 38 to 17 per 1,000 live births. However, sepsis continues to be a prominent challenge, accounting for 30–50% of neonatal deaths [1, 2]. In Tanzania, sepsis still contributes to 29% of neonatal fatalities, emphasizing the critical need for improved early-onset sepsis management [3]. Currently, the main initial treatment for sepsis in newborns is intravenous administration of antibiotics that target both Gram-negative and Gram-positive bacteria [4]. The World Health Organization recommends gentamicin in combination with a beta-lactam such as ampicillin [4]. While gentamicin remains widely effective, providing strong coverage against Gram-negative bacteria, it has a narrow therapeutic index and thus carries a risk of nephrotoxicity and ototoxicity, particularly when treatment extends beyond 48 hours and therapeutic drug monitoring (TDM) is unavailable [5, 6]. In such situations, up to 8% of exposed neonates may experience subclinical or overt acute kidney injury (AKI), which could lead to chronic kidney disease and/or irreversible hearing loss [7].

In Tanzania, national guidelines recommend a once-daily gentamicin regimen of 4 to 5 mg/kg in combination with Ampicillin-Cloxacillin [8]. The 5 mg/kg dosing strategy is designed to achieve sufficient bactericidal peak concentrations while avoiding high trough concentrations, which are associated with a high risk of nephrotoxicity and ototoxicity [9]. Traditionally, however, gentamicin has been administered at a dose of 4 mg/kg once daily. The 5 mg/kg dose is supported by evidence from pharmacokinetic modeling, extended-interval dosing (individualized dosing intervals tailored to gestational age and renal function) studies, and cohort comparisons of the 5 mg/kg and 4 mg/kg doses, showing that the 5 mg/kg dose achieves better peak concentrations without increasing toxicity.

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Aminoglycoside antibiotics like gentamicin exhibit concentration-dependent killing and a post-antibiotic effect; thus, higher peaks associated with a large once-daily dose are more effective than lower peaks achieved with smaller repeated doses. However, some studies have reported that 5 mg/kg once-daily dosing results in high trough concentrations, increasing the likelihood of toxicity, particularly when therapeutic drug monitoring is unavailable [10–12]. Historically, the 4 mg/kg regimen was considered safer due to lower systemic exposure; however, concerns have been raised that this lower dose may fail to achieve optimal peak concentrations required for severe neonatal infections. In response to these efficacy concerns, clinicians in many settings prefer the higher 5 mg/kg dose to the 4mg/kg dose in order to ensure adequate bactericidal activity. Conversely, more recent evidence suggests that a once-daily 4 mg/kg regimen can maintain both peak and trough concentrations within accepted therapeutic ranges, potentially reducing the risk of gentamicin-associated toxicity while preserving efficacy [13–16]. Despite these findings, the lower-dose regimen remains underutilized in many local settings, and robust comparative safety data in real-world neonatal populations remain limited.

In resource-limited settings, therapeutic drug monitoring is not routinely available, and monitoring renal function during treatment is often challenging. Nevertheless, the 5 mg/kg once-daily dose regimen is recommended and widely used in clinical practice. However, this regimen has been shown to be associated with high trough concentrations in some studies, suggesting an increased risk of nephrotoxicity and/or ototoxicity. Indeed, we have observed high peak and trough concentrations, and associated AKI among term neonates treated with gentamicin using this approach (James et al) [10]. Although used less frequently than the 5 mg/kg regimen, the 4 mg/kg once-daily dose is also part of routine clinical prescribing practices in some settings, typically depending on clinician judgment and patient-specific considerations. However, comparative safety data between these dosing strategies remain limited, particularly in real-world neonatal populations, warranting further investigation.

Therefore, this study aimed to determine the incidence of nephrotoxicity, characterized by renal tubular injury (increase in urinary Kidney Injury Molecule-1 concentration) or renal function decline (change in serum creatinine concentration following gentamicin exposure), and the incidence of ototoxicity, characterized by inner-ear injury (high-frequency hearing loss and/or balance dysfunction), among term neonates receiving once-daily intravenous gentamicin at 4 mg/kg or 5 mg/kg. By generating local safety data, the findings contribute to the choice of an evidence-based optimal dosing strategy, especially in resource-limited settings.

Methods

Study design, and setting

This was a three-group prospective observational cohort study involving term neonates admitted to Mwananyamala Regional Referral Hospital (MRRH) in Dar es Salaam with suspected sepsis, from January to March 2025. MRRH admits approximately 400 neonates per month and is staffed by qualified and experienced healthcare providers, including pediatricians. The facility is supported by a clinical laboratory capable of performing essential hematological and clinical chemistry analyses, including serum creatinine measurement.

Eligible participants received antibiotic therapy as part of routine clinical care and were subsequently classified into three groups: gentamicin 5 mg/kg once daily or gentamicin 4 mg/kg once daily plus Ampiclox (ampicillin 50 mg/kg plus cloxacillin 50 mg/kg); or a comparison group: receiving ceftriaxone 50 mg/kg once daily (for suspected meningitis without jaundice) or cefotaxime 50 mg/kg twice daily (in cases with jaundice). Following baseline assessment, all participants were followed up for 7 days, with renal tubular injury test (uKIM-1) performed at baseline (and on day 2; renal function test (serum creatinine) and ototoxicity at baseline and on day 7.

Study population and sample size estimation

The study enrolled term-neonates (gestational age ≥37 weeks), as determined by last menstrual period, who had a clinical diagnosis of neonatal sepsis on admission, aged 1 to 28 days, and for whom a written informed consent from the mother or care taker was obtained. Term-neonates who were severely ill in decompensated states including respiratory distress, lethargy, coma, shock, and those with hyperbilirubinemia, or requiring calcium-containing IV fluids were excluded. Also excluded, were term-neonates with severe congenital malformations, exposure to nephrotoxic or ototoxic medications (for example, vancomycin, furosemide, acyclovir, amphotericin B, and ibuprofen) or drugs with potential pharmacokinetic interactions with gentamicin (such as phenobarbital, erythromycin, phenytoin) within 72 hours prior to admission, and those with elevated serum creatinine or evidence of hearing loss at baseline or prior gentamicin therapy within the past 72 hours preceding study enrollment.

Because of the lack of data on the incidence of gentamicin-induced acute kidney injury (AKI) or ototoxicity stratified by specific gentamicin doses (5 mg/kg vs 4 mg/kg), the single-proportion formula (Fisher and Leslie method) was used to estimate the required sample size for each study group individually, assuming a cumulative incidence (risk) of 8% [7] and a desired margin of error of 5%. Adjusting for a 10% dropout rate, the minimum sample size for each group was calculated to be 125.

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Recruitment and drug administration

Eligible neonates were consecutively enrolled upon admission and categorized according to the antibiotic regimen they were to receive as part of routine clinical care. Treatment decisions, including the choice of antibiotic and gentamicin dose (5 mg/kg once daily or 4 mg/kg once daily), were made solely by the attending clinicians in accordance with standard hospital prescribing practices, without any investigator influence or assignment.

Each participant was assigned a unique study identification number, which was used throughout the study for data collection, analysis, and reporting to ensure confidentiality.

Gentamicin (5 mg/kg or 4 mg/kg) was administered once daily as an intravenous bolus injection. Ampiclox (ampicillin 50 mg/kg plus cloxacillin 50 mg/kg) was administered twice daily as an intravenous bolus injection. Ceftriaxone was administered at 50 mg/kg every 24 hours as a slow intravenous injection whereas Cefotaxime was administered at 50 mg/kg every 12 hours as a short intravenous infusion, according to standard neonatal dosing schedules.

Serum creatinine and urinary kidney injury molecule-1 measurement

Blood samples for serum creatinine measurement (0.5 mL) were collected via heel prick from each participant at baseline, prior to initiation of antibiotic therapy, and on day 7 of treatment. Samples were collected into sterile serum separator tubes and labeled with participant identifiers, including study number, study group, date and time of collection, and mother's initials, and immediately transferred to the MRRH laboratory for processing and analysis.

At the laboratory, serum was transferred into eppendorf microcentrifuge tubes and centrifuged at 3,000 × g for 10 minutes to separate serum from cellular components. Serum creatinine was subsequently measured using a fully automated Erba XL-100 clinical chemistry analyzer (Erba Mannheim, Mannheim, Germany) in accordance with standard laboratory protocols.

Urine samples (2 mL) were collected from all participants to measure urinary Kidney Injury Molecule-1 (uKIM-1), which serves as a sensitive biomarker for proximal tubular injury. Baseline urine was obtained either prior to antibiotic initiation, if the neonate had voided into the diaper, or within four hours after the first antibiotic dose. Subsequent urine sampling was performed on day 2 according to treatment regimen. In neonates receiving gentamicin (5 mg/kg and 4 mg/kg once daily) and in those receiving once-daily ceftriaxone, samples were collected 2 hours after the third dose. In neonates receiving twice-daily cefotaxime, samples were collected 2 hours after the fifth dose. Cotton wool balls placed in the perineal region were used for urine collection, ensuring that fecal contamination was avoided. Once collected, urine was gently expressed into sterile containers, labeled, and transferred to the laboratory immediately. The samples were then centrifuged at 2000 × g for 10 minutes, aliquoted into 0.5 mL portions, and stored at –80°C until analysis in batches. Levels of uKIM-1 were quantified using a validated sandwich enzyme-linked immunosorbent assay (ELISA) kit (R&D Systems, Minneapolis, MN, USA) in pre-defined batches every three days to reduce inter-assay variability and uphold analytical consistency.

Assessment of ototoxicity using automated auditory brainstem response (AABR)

Inner ear injury was assessed using Automated Auditory Brainstem Response (AABR) testing at baseline and on day 7 from start of treatment. Automated hearing threshold estimation was performed under standardized conditions in the neonatal unit at MRRH by a trained care provider using the Sentiero Advanced system (PATH MEDICAL GmbH, Germany). Hearing threshold shift of ≥20 dB from baseline was considered indicative of ototoxicity, consistent with the American Speech-Language-Hearing Association (ASHA) ototoxicity monitoring criteria.

Data Collection

Data were collected by trained research assistants and nurses at the neonatal unit using specially designed, pretested, case report forms (CRF) under the supervision of MJ. All clinical study specific data were recorded on the CRF at the point of collection or measurement. Data were entered into a secure electronic database using a double-entry process to minimize transcription errors, and MJ conducted weekly random audits of a sample of CRFs to verify accuracy.

Data analysis

Data were analyzed using IBM SPSS Statistics version 27.0. Descriptive statistics were used to summarize the socio-demographic and clinical characteristics of study participants. Categorical variables were presented as frequencies and percentages, while continuous variables were summarized using median and interquartile range (IQR), as the data were not normally distributed. Baseline covariate distributions across study groups were compared using the Chi-square test or Fisher's exact test for categorical variables and the Kruskal–Wallis test for continuous variables. The Wilcoxon signed-rank test was used to compare pre- and post-treatment measurements within the same participants for serum creatinine, uKIM-1 concentrations, and AABR thresholds, while the Mann–Whitney U test was used to compare non-normally distributed continuous variables between two independent study groups, where applicable. A Generalized Estimating Equation (GEE) linear regression model was used to evaluate the association between study groups and automated auditory brainstem

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response (AABR) thresholds while accounting for within-subject correlations due to repeated measurements. Statistical significance was determined using a two-sided p-value of <0.05.

Results

A total of 493 neonates were screened for eligibility. Of these, 118 (23.9%) were excluded for various reasons, most commonly because they had received gentamicin within three days prior to admission. Three hundred and seventy-five neonates (76.1%) met all inclusion criteria and none of the exclusion criteria and were enrolled in the study, 125 on each of the three groups of the study (**Figure 1**). No participants withdrew consent, died or were lost to follow-up. All participants provided blood and urine samples at baseline and after gentamicin therapy. All participants were treated to completion with the initially prescribed gentamicin dose, with no requirement for dose escalation, treatment switching, or addition of other antibiotics.

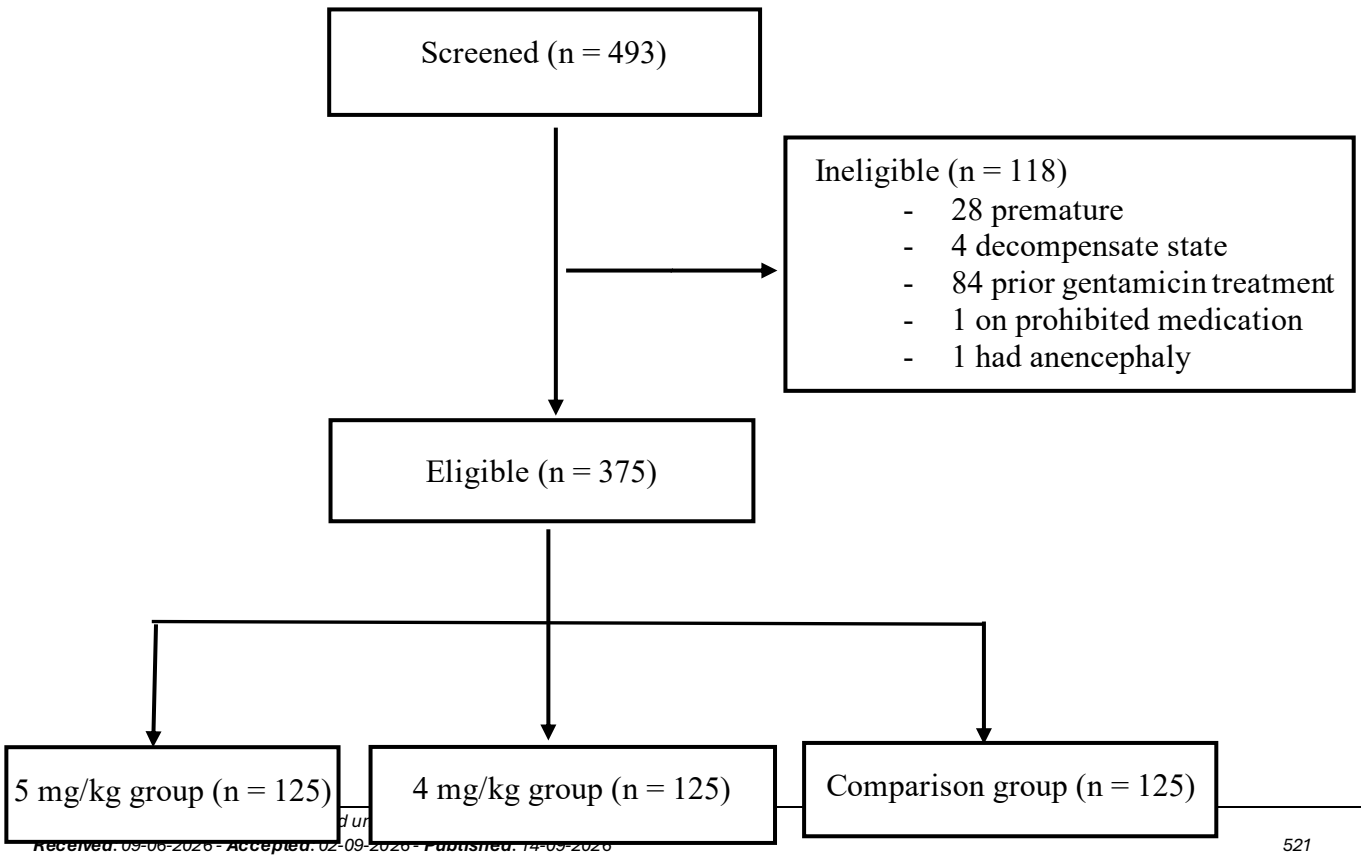

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Figure 1: Participants' screening, eligibility and recruitment.

Baseline social demographic and clinical data

Most participants had normal birth weight and normal weight at enrolment, with no statistically significant differences observed across the three study groups. Age distribution and APGAR scores were also comparable between groups. However, the proportion of participants with diarrhea was significantly higher in the 5 mg/kg group compared with the other two study groups, while the proportion of participants with vomiting did not differ significantly across groups. The majority of participants in all three study groups were able to suck, and there was no significant difference in the proportion of participants unable to suck. Overall, participants across the three study groups were comparable in other baseline characteristics, including the absence of evidence of nephrotoxicity and inner-ear hearing loss, which were part of the inclusion criteria (**Table 1**).

Table 1. Baseline characteristics of the study participants

Variable	Study group			p – value
	5mg/kg (n = 125)	4mg/kg (n = 125)	Comparison group	
Median age (IQR) (days)	8 (6, 11)	8 (6, 11)	8 (6, 9)	0.378
Sex, n (%)				
Male	78 (62.4)	72 (57.6)	54 (43.2)	0.007
Female	47 (37.6)	53 (42.4)	71 (56.8)	
Median gestational age (weeks) (IQR)	38 (37, 38)	38 (37, 38)	38 (37, 38)	0.962
Median birth weight in Kg (IQR)	3.0 (2.8, 3.5)	3.0 (2.6, 3.4)	3.0 (2.6, 3.4)	0.427
Median weight at enrolment in Kg (IQR)	3.10 (2.4, 3.2)	3.04 (2.4, 3.6)	3.07 (2.3, 3.8)	0.49
Weight at enrolment category, n (%)				
Normal (≥ 2.5 kg)	100 (80.0)	96 (76.8)	101 (80.8)	0.712
Low (< 2.5 kg)	25 (20.0)	29 (23.2)	24 (19.2)	
Median height in cm (IQR)	50.0 (48.5, 52.0)	50.0 (48.0, 52.3)	50.0 (48.0, 52.8)	0.696
Median Apgar score (IQR)	8.0 (7.0, 9.0)	8.0 (7.0, 8.5)	8.0 (7.0, 8.5)	0.222
Diarrhea, n (%)				
Yes	24 (19.2)	11 (8.8)	7 (5.6)	0.002
No	101 (80.8)	114 (91.2)	118 (94.4)	
Vomiting, n (%)				
Yes	27 (21.6)	24 (19.2)	26 (20.8)	0.892
No	98 (78.4)	101 (80.8)	99 (79.2)	
Unable to suck, n (%)				
Yes	10 (8.0)	14 (11.2)	15 (12.0)	0.548
No	115 (92.0)	111 (88.8)	110 (88.0)	
Median creatinine (µmol/L) (IQR)	79.0 (56.9, 99.1)	80.0 (60.0, 100)	78.5 (62.9, 100)	0.819
Median urinary KIM-1 (ng/mL) (IQR)	0.38 (0.28, 0.51)	0.39 (0.29, 0.50)	0.39 (0.30, 0.45)	0.594
Median AABR threshold (dB) (IQR)	7.0 (5.0, 9.0)	7.0 (4.0, 9.0)	6.0 (4.5, 9.0)	0.389
Median baseline eGFR (IQR)	25.9 (20.2, 34.5)	24.4 (19.9, 33.1)	25.6 (20.7, 33.3)	0.854

Tubular injury and renal function decline (nephrotoxicity)

In the 4 mg/kg group, median (IQR) serum creatinine increased from 80.0 (60.0–100.0) µmol/L at baseline to 89.0 (66.0–120.0) µmol/L after treatment ($p < 0.001$). Similarly, in the 5 mg/kg group, median (IQR) serum creatinine increased from 79.0 (56.9–99.1) µmol/L at baseline to 127.0 (67.0–140.0) µmol/L after treatment ($p < 0.001$). In contrast, the comparison group showed a decrease in median (IQR) serum creatinine from 78.5 (62.9–100) µmol/L at baseline to 75 (61.0–90.0) µmol/L after treatment ($p = 0.003$) (**Figure 2**).

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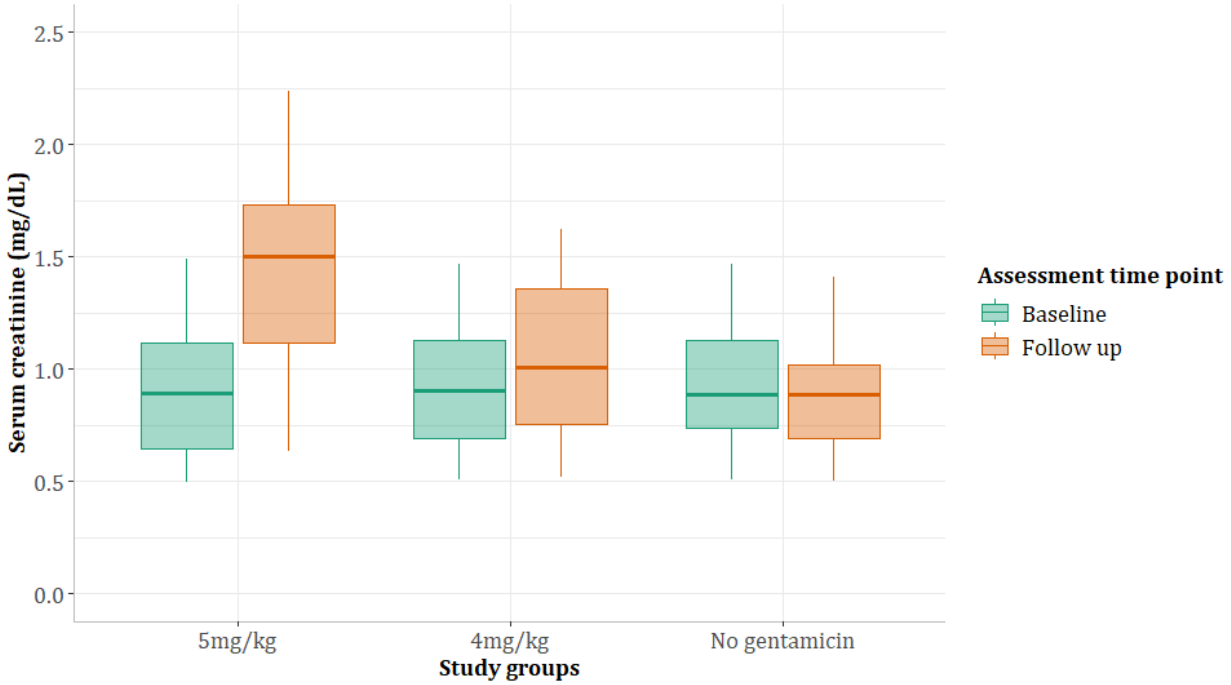

Figure 2: Changes in serum creatinine before and after treatment across study groups

Consistent with these findings, elevated urinary KIM-1 levels were observed in 52.8% of neonates in the 5 mg/kg group, 4.0% in the 4 mg/kg group, and none in the comparison group, indicating a higher occurrence of early renal tubular injury among neonates receiving the higher gentamicin dose. Similarly, elevated serum creatinine levels were observed in 51.2% of neonates in the 5 mg/kg group, compared with 2.4% in the 4 mg/kg group and none in the comparison group (**Table 2**), suggesting a dose-related effect of gentamicin on renal function.

Consistent with these findings, a significantly higher proportion of participants in the 5 mg/kg group developed nephrotoxicity compared with the 4 mg/kg group, while no participants in the comparison group developed nephrotoxicity. In the 5 mg/kg group, 1.6% of participants developed subclinical nephrotoxicity (elevated uKIM-1 without a corresponding rise in serum creatinine), whereas 51.2% developed overt nephrotoxicity (elevations in both uKIM-1 and serum creatinine). In contrast, in the 4 mg/kg group, similarly, 1.6% of participants developed subclinical nephrotoxicity, whereas only 2.4% developed overt nephrotoxicity (**Table 2**).

Table 2: The relationship between study group and the development of nephrotoxicity

	Nephrotoxicity status			
Variable	**None (%)**	**Subclinical (%)**	**Overt (%)**	**p – value**
Study group				
5mg/kg	59 (47.2)	2 (1.6)	64 (51.2)	< 0.001
4mg/kg	120 (96)	2 (1.6)	3 (2.4)	
Comparison	125 (100.0)	0 (0.0)	0 (0.0)	

The incidence of AKI

According to KDIGO criteria, AKI occurred more frequently in the 5 mg/kg group than in the 4 mg/kg group. In the 5 mg/kg group, 44 participants (35.2%) developed stage I AKI (1.5–1.99-fold increase in serum creatinine), 18 (14.4%) developed stage II (2.0–2.99-fold increase), and 2 (1.6%) developed stage III (>3-fold increase). In contrast, only 3 participants (2.4%) in the 4 mg/kg group developed stage I AKI, with no participants developing stage II or III. On the other hand, no participant developed AKI in the comparison group. All participants meeting KDIGO criteria for AKI also had elevated urinary kidney injury molecule-1 (uKIM-1 >1 ng/mL), supporting the presence of overt nephrotoxicity characterized by both tubular injury and renal function impairment (**Table 3**). With a substantially higher incidence of AKI observed in the 5 mg/kg group, our findings demonstrate a clear dose-dependent increase in gentamicin-associated nephrotoxicity in neonates exposed to gentamicin.

Table 3: The relationship between study group and development of AKI

	Acute Kidney Injury (AKI)				
Variable	**No AKI (%)**	**Stage 1 (%)**	**Stage 2 (%)**	**Stage 3 (%)**	**p – value**

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Study group					
5 mg/kg	61 (48.8)	44 (35.2)	18 (14.4)	2 (1.6)	< 0.001
4 mg/kg	122 (97.6)	3 (2.4)	0 (0.0)	0 (0.0)	
Comparison	125 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	

Changes in Automated Auditory Brainstem Response (ototoxicity)

At baseline, all study groups had low AABR thresholds consistent with normal hearing sensitivity (<25 dB). In the GEE analysis, both gentamicin groups had slightly lower baseline AABR thresholds compared with the comparison group (5 mg/kg: cβ = -2.18, 95% CI: -3.46 to -0.91, p < 0.001; 4 mg/kg: cβ = -1.01, 95% CI: -1.94 to -0.08, p = 0.034) (**Table 4**).

There was a significant interaction between study group and follow-up time, indicating that changes in AABR thresholds over time differed across groups. Compared with the comparison group, participants receiving 5 mg/kg gentamicin showed an average increase of 2.46 units in AABR thresholds over time (95% CI: 1.52 to 3.39, p < 0.001), while those receiving 4 mg/kg gentamicin showed an increase of 0.98 units (95% CI: 0.67 to 1.30, p < 0.001). In contrast, AABR thresholds decreased over time in the comparison group. Overall, while all groups had normal hearing thresholds at baseline, neonates receiving gentamicin demonstrated increases in AABR thresholds over time, indicating reduced hearing sensitivity, whereas the comparison group showed improvement. Notably, only neonates in the 5 mg/kg group experienced threshold shifts greater than 20 dB from baseline, consistent with ASHA-defined ototoxicity.

Table 4: Association between study group and AABR thresholds from GEE analysis

Variable	cβ	95% CI	p – value
Time of follow up	-0.64	-0.94 – -0.34	< 0.001
Study group			
5 mg/kg	-2.18	-3.46 – -0.91	< 0.001
4 mg/kg	-1.01	-1.94 – -0.08	0.034
Comparison	Ref		
Study group * Time of follow up			
5 mg/kg	2.46	1.52 – 3.39	< 0.001
4 mg/kg	0.98	0.67 – 1.30	< 0.001
Comparison	Ref		

Key: cβ = Beta coefficient; CI = confidence interval; Ref = reference category

Note: Coefficients represent differences in AABR thresholds (dB). The comparison group was used as the reference category. The study group coefficients reflect baseline differences relative to the comparison group. The interaction term (study group × time of follow-up) represents differences in the change of AABR thresholds over time between groups. Positive coefficients indicate an increase in AABR thresholds (worsening hearing sensitivity), while negative coefficients indicate lower thresholds (better hearing sensitivity). Statistical significance was set at p < 0.05.

The incidence of Ototoxicity

Following treatment, 5/125 (4.0%) of neonates in the 5 mg/kg group exhibited elevated AABR thresholds consistent with ASHA-defined ototoxic change, whereas all participants in the 4 mg/kg group and the comparison group remained within normal limits. These findings suggest a possible dose-related effect of gentamicin on ototoxicity, with the 5 mg/kg regimen associated with a higher observed risk.

Discussion

Guideline recommended dosing of gentamicin in neonates is between 4mg/kg and 5mg/kg once daily. There is pharmacokinetic evidence to suggest that the 5mg/kg dose results into high peak concentrations that are critical for efficacy while maintaining trough concentrations that are not high enough to cause toxicity. These are considered to be advantages of this dosage regimen over the traditional 4mg/kg, which is thought not to guarantee high enough peaks for efficacy. Experience in Tanzania show that the 5mg/kg is preferred and prescribed more often than the 4mg/kg. However, in some studies the 5mg/kg dose has been shown to results into trough concentrations in the toxicity range associated with AKI [10-12].

Despite this, direct comparative evidence remains limited. This study addresses this gap by providing a head-to-head safety evaluation of the two dosing strategies in a real-world neonatal population where nephrotoxicity and ototoxicity risk associated with once-daily intravenous gentamicin administered at 5 mg/kg and 4 mg/kg alongside a comparison group receiving non-nephrotoxic antibiotics has been assessed. Although available evidence favors the 5mg/kg daily dose as the effective and safe approach, data from our study show that this may not apply in every setting. We have observed a significantly higher risk of renal tubular injury and renal function decline in the 5mg/kg than in the 4mg/kg dose. Similarly, a

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higher proportion of neonates receiving the 5 mg/kg dose developed increases in serum creatinine consistent with KDIGO stage I AKI compared with those receiving 4 mg/kg.

These findings align with previous reports linking elevated gentamicin trough concentrations (>2 µg/mL) to nephrotoxicity in neonates, particularly when therapy extends beyond 48 hours and the dosing not tailored to serum creatinine or therapeutic drug monitoring [5, 7]. The mechanistic basis for this toxicity is well established: gentamicin undergoes glomerular filtration and accumulates within proximal tubular epithelial cells through receptor-mediated endocytosis, where it triggers oxidative stress, lysosomal rupture, and apoptotic or necrotic tubular cell death [17, 18]. The dose-dependent pattern of nephrotoxicity observed in this study mirrors prior clinical observations by James et al. [10] and Hayani et al. [11], underscoring the need for looking into an optimal extended-interval dosing strategy for resource-limited settings.

In contrast, neonates who received 4 mg/kg gentamicin exhibited a modest, but statistically significant, serum creatinine increase**,** with only 2.4% meeting the KIDGO Stage I AKI criteria. This markedly lower incidence compared with the 5mg/kg dose, demonstrates a safer renal profile at the reduced dose, consistent with pharmacokinetic evidence highlighted by Krishnan and George [13], Shabuj et al. [14], Serane et al. [15] and Saad [16], supporting 4 mg/kg regimens to balance antimicrobial efficacy and toxicity risk.

However, reliance on serum creatinine alone may underestimate early renal injury in neonates, given their low muscle mass and the confounding influence of maternal creatinine transfer [19]. To address this limitation, uKIM-1 was concurrently measured. Following treatment, about 51% of neonates in the 5 mg/kg group showed early proximal tubular injury preceding or accompanying renal function decline. In the 4 mg/kg group, only about 2 % of the neonates had early proximal tubular injury supporting better renal safety of the lower dosing regimen. While serum creatinine reflects functional impairment, uKIM-1 detects structural tubular injury at an earlier stage, potentially providing an opportunity for timely intervention before irreversible damage occurs [20].

None of the neonates in the comparison group developed early proximal tubular injury, suggesting that the observed renal impairment in the gentamicin-treated groups was most likely gentamicin-induced rather than attributable to systemic illness or supportive neonatal care. This stability supports an association between gentamicin exposure and renal injury.

In conclusion, these findings confirm that in some settings the 5 mg/kg dosing may carry more risk for nephrotoxicity, while 4 mg/kg dosing offers a safer renal profile. This means that in the setting of limited therapeutic drug monitoring, the 4mg/kg daily dose is the safer option, and when the 5mg/kg dose is chosen, the dosing interval should be tailored to gestational age and baseline serum creatinine clearance (with extended-interval dosing in mind, 36 to 48 hours in some circumstances) in order to lower the overall exposure of the kidneys and inner ear to the drug.

This study also evaluated potential ototoxic effects of once-daily intravenous gentamicin using individual level AABR threshold changes (ASHA) following gentamicin exposure. While the neonates in the comparison group showed improvement in AABR threshold after treatment, 4% of the neonates on gentamicin 5mg/kg dose showed ototoxicity, and in all of the participants on the gentamicin 4mg/kg dose, AABR threshold remained within normal limit and thus, developed no ototoxicity. Also this confirms a dose-dependent ototoxicity associated with gentamicin exposure. With this regard, the 4mg/kg dose also appears to be safer than the 5mg/kg dose.

Our findings are consistent with prior studies by Naeimi et al. [21] and Vella-Brincat et al. [22], which reported increased hearing impairment in neonates receiving gentamicin doses exceeding 4 mg/kg daily, as measured by auditory evoked potentials. Similarly, El-barbary et al. [23] demonstrated that ototoxicity risk increases with higher cumulative gentamicin exposure and elevated serum peak and trough concentrations. Conversely, studies supporting 4 mg/kg dosing regimens, including those by Baggio et al. [24] and Rameshsankar et al. [25], found minimal or no significant auditory effects, consistent with the safer profile observed in the 4mg/kg group in this study.

The slight improvement in AABR thresholds observed in the comparison group likely reflects normal auditory pathway maturation or the resolution of transient conductive conditions rather than drug effects. This further underscores that gentamicin-associated ototoxicity is a specific pharmacologic effect, not a general consequence of systemic illness or intravenous antibiotic use.

Clinically, our data suggest that 4 mg/kg gentamicin dosing may offer a more favorable ototoxicity profile compared with 5 mg/kg. However, inter-individual pharmacokinetic variability can still result in elevated drug exposure, even at lower doses. Therefore, careful dosing and, where feasible, therapeutic drug monitoring should be prioritized to minimize ototoxic risk.

Study strengths and Limitations

A major strength of this study is its prospective design, relatively large sample size, and direct comparison of two commonly used gentamicin dosing regimens. Unlike many previous studies that have focused mainly on pharmacokinetic outcomes or assessed toxicity without direct dose comparisons, this study provides real-world evidence on the renal and auditory safety of different gentamicin dosing strategies. These findings are particularly relevant in resource-limited settings where therapeutic drug monitoring is not routinely available and clinicians must balance effective bacterial killing with the risk of toxicity when selecting gentamicin regimens.

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However, some limitations should be considered. First, the 7-day follow-up period may not have captured delayed or cumulative gentamicin-associated nephrotoxicity and ototoxicity, as some patients may develop adverse effects after a longer observation period, including up to 14 days following exposure. Second, the single-center design may limit the generalizability of the findings to other neonatal populations with different demographic and clinical characteristics.

Conclusion

Administration of gentamicin at 5 mg/kg once daily in term neonates is associated with increased renal and auditory toxicity. In contrast, the 4 mg/kg regimen may have a more favorable safety profile, with lower risk of gentamicin-induced nephrotoxicity and ototoxicity than the 5mg/kg regimen. These findings support a dose-dependent pattern of gentamicin-associated nephrotoxicity and ototoxicity in neonates and highlight the need for individualized dosing guided by serum creatinine monitoring and, where available, therapeutic drug monitoring to optimize efficacy and safety.

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Competing interests

The authors declare that they have no competing interest.

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Ethics approval and consent to participate

The study was conducted in accordance with the principles of the Declaration of Helsinki. Ethical clearance was obtained from the University of Dodoma (UDOM) Institutional Research Review Ethics Committee (IRREC) (MA.84/261/74/38), and permission to conduct the study was granted by the Medical Officer in charge of Mwananyamala Regional Referral Hospital (MRRH) (MA.240/341/01/38), Dar es Salaam, where the study was carried out. Written informed consent was obtained from each mother prior to enrollment of her neonate. Each participant was assigned a unique study identification number, which was used throughout the study (including data collection, analysis, presentation, and reporting) to ensure confidentiality.

Author contributions

MEJ, PS, AL, and DB contributed to the conception and design of the study. MEJ was responsible for data collection, data analysis, and drafting of the manuscript. PS, AL, and DB supervised the study and critically reviewed the manuscript for important intellectual content. PK contributed to data analysis and interpretation of results. All authors have read and approved the final version of the manuscript.

Availability of data and materials

The datasets generated and/or analyzed during the current study are not publicly available to preserve participant confidentiality but can be obtained from the corresponding author on reasonable request.

References

1. Alexander M, Alkema L. Global estimation of neonatal mortality using a Bayesian hierarchical splines regression model. *Demogr Res*. 2018;38(1):335–72.
2. Jabiri A, Wella HL, Semiono A, et al. Prevalence and factors associated with neonatal sepsis among neonates in Temeke and Mwananyamala Hospitals in Dar es Salaam, Tanzania. *Tanzan J Health Res*. 2016;18(4):1–7.
3. Manji K. Situation analysis of newborn health in Tanzania. 2009;07–10.
4. Obiero CW, Seale AC, Berkley JA. Empiric treatment of neonatal sepsis in developing countries. *Pediatr Infect Dis J*. 2015;34(6):659–61.
5. Pacifici GM, Marchini G. Clinical pharmacokinetics of gentamicin in neonates. *Int J Pediatr*. 2017;5(3):4575–99.
6. Musiime GM, Seale AC, Moxon SG, Lawn JE. Risk of gentamicin toxicity in neonates treated for possible severe bacterial infection in low- and middle-income countries: systematic review. *Trop Med Int Health*. 2015;20(12):1593–606.
7. Lopez-Novoa JM, Quiros Y, Vicente L, Morales AI, Lopez-Hernandez FJ. New insights into the mechanism of aminoglycoside nephrotoxicity: an integrative point of view. *Kidney Int*. 2011;79(1):33–45. doi:10.1038/ki.2010.337.
8. National Medicine and Therapeutic Committee. Standard Treatment Guidelines Tanzania. 6th ed. 2021:596. Available from: https://medicine.st-andrews.ac.uk/igh/wp-content/uploads/sites/44/2022/01/STG-NEMLIT-2021.pdf

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9. English M, et al. A randomised, controlled trial of once daily and multi-dose daily gentamicin in young Kenyan infants. *Arch Dis Child*. 2004;89(7):665–9. doi:10.1136/adc.2003.032284.
10. James ME, Naburi H, Mugusi S, et al. Gentamicin concentration and acute kidney injury in term neonates treated for neonatal sepsis with gentamicin and ampicillin-cloxacillin combination. Antimicrob Agents Chemother. 2024;68(6). doi:10.1128/aac.01495-23
11. Hayani KC, Hatzopoulos FK, Frank AL, et al. Pharmacokinetics of once-daily dosing of gentamicin in neonates. J Pediatr. 1997;131(1 I):76–80.
12. Hollander EM, van Tuinen EL, Schölvinck EH, et al. Evaluation of dosing guidelines for gentamicin in neonates and children. Antibiotics (Basel). 2023;12(5). doi:10.3390/antibiotics12050810
13. Krishnan L, George SA. Gentamicin therapy in preterms: a comparison of two dosage regimens. Indian Pediatr. 1997;34(12):1075–80.
14. Shabuj MKH, Moni SC, Shaha CK, et al. Gentamicin in newborn sepsis: once-daily versus twice-daily dose. Bangladesh Med Res Counc Bull. 2017;43(2):82–6.
15. Serane TV, Zengeya S, Penford G, et al. Once daily dose gentamicin in neonates – is our dosing correct? Acta Paediatr. 2009;98(7):1100–5.
16. Saad AA. Once daily gentamicin dosing in full term neonates. 2003;966(June):978–81.
17. McWilliam SJ, Antoine DJ, Sabbisetti V, Turner MA, Farragher TV, Bonventre JV, et al. Mechanism-based urinary biomarkers to identify the potential for aminoglycoside-induced nephrotoxicity in premature neonates: a proof-of-concept study. *PLoS One*. 2012;7(8):e41450.
18. Huth ME, Ricci AJ, Cheng AG. Mechanisms of aminoglycoside ototoxicity and targets of hair cell protection. *Int J Otolaryngol*. 2011;2011:1–19.
19. Ostermann M, Joannidis M. Acute kidney injury 2016: diagnosis and diagnostic workup. *Crit Care*. 2016;20(1):1–13. doi:10.1186/s13054-016-1478-z.
20. Sridharan K, Jufairi MAL, Segai OAL, et al. Biomarkers in neonates receiving potential nephrotoxic drugs. 2021;7078–88.
21. Naeimi M, Maamouri G, Boskabadi H, et al. Assessment of aminoglycoside-induced hearing impairment in hospitalized neonates by TEOAE. *Indian J Otolaryngol Head Neck Surg*. 2009;61(4):256–261. doi:10.1007/s12070-009-0078-5.
22. Vella-Brincat JWA, Begg EJ, Robertshawe BJ, et al. Are gentamicin and/or vancomycin associated with ototoxicity in the neonate? A retrospective audit. *Neonatology*. 2011;100(2):186–193. doi:10.1159/000324857.
23. El-Barbary MN, Ismail RIH, Ibrahim AAA. Gentamicin extended interval regimen and ototoxicity in neonates. *Int J Pediatr Otorhinolaryngol*. 2015;79(8):1294–1298. doi:10.1016/j.ijporl.2015.05.036.
24. Baggio CL, da Silveira AF, Hyppolito MA, et al. A functional study on gentamicin-related cochleotoxicity in its conventional dose in newborns. *Braz J Otorhinolaryngol*. 2010;76(1):91–95. doi:10.1590/s1808-86942010000100015.
25. Rameshsankar S, Seethapathy J, Balakrishnan U. Ototoxic drug exposure and hearing loss in neonates: a scoping review. *Am J Audiol*. 2024;33(4):1356–1377. doi:10.1044/2024_AJA-24-00065.

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