

Recommendations of Gentamicin Dose Based on Different Pharmacokinetic/Pharmacodynamic Targets for Intensive Care Adult Patients: A Redefining Approach

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Background: In addition to the maximum plasma concentration (C_{max}) to the minimum inhibitory concentration (MIC) ratio, the 24-hour area under the concentration-time curve (AUC_{24h}) to MIC has recently been suggested as pharmacokinetic/pharmacodynamic (PK/PD) targets for efficacy and safety in once-daily dosing of gentamicin (ODDG) in critically ill patients.

Purpose: This study aimed to predict the optimal effective dose and risk of nephrotoxicity for gentamicin in critically ill patients for two different PK/PD targets within the first 3 days of infection.

Methods: The gathered pharmacokinetic and demographic data in critically ill patients from 21 previously published studies were used to build a one-compartment pharmacokinetic model. The Monte Carlo Simulation (MCS) method was conducted with the use of gentamicin once-daily dosing ranging from 5–10 mg/kg. The percentage target attainment (PTA) for efficacy, $C_{max}/MIC \sim 8$ –10 and $AUC_{24h}/MIC \geq 110$ targets, were studied. The $AUC_{24h} > 700$ mg·h/L and $C_{min} > 2$ mg/L were used to predict the risk of nephrotoxicity.

Results: Gentamicin 7 mg/kg/day could achieve both efficacy targets for more than 90% when the MIC was < 0.5 mg/L. When the MIC increased to 1 mg/L, gentamicin 8 mg/kg/day could reach the PK/PD and safety targets. However, for pathogens with MIC ≥ 2 mg/L, no studied gentamicin doses were sufficient to reach the efficacy target. The risk of nephrotoxicity using $AUC_{24h} > 700$ mg·h/L was small, but the risk was greater when applying a C_{min} target > 2 mg/L.

Conclusion: Considering both targets of $C_{max}/MIC \sim 8$ –10 and $AUC_{24h}/MIC \geq 110$, an initial gentamicin dose of 8 mg/kg/day should be recommended in critically ill patients for pathogens with MIC of ≤ 1 mg/L. Clinical validation of our results is essential.

Keywords: gentamicin, C_{max}/MIC , AUC_{24h}/MIC , nephrotoxicity, critically ill

Introduction

Gentamicin is an aminoglycoside antibiotic which effectively treats serious Gram-negative infections.¹ In addition, global Gram-negative resistance rates are increasing and there is limited availability of antibiotics to treat the emergence of resistance.² An appropriate empirical dose of gentamicin can be suggested based on local epidemiological data and susceptibility patterns. Critical illness and severe infection lead to altered pathophysiology and gentamicin pharmacokinetics. Increased volume of distribution (V_d) is frequently reported in critically ill patients.^{2,3} Furthermore, augmented renal clearance of gentamicin in patients with sepsis, severe trauma, undergone major surgeries, or use of inotropic agents also plays a role in an alteration of gentamicin pharmacokinetics.⁴ Therefore, appropriate dosing regimens of gentamicin in a timely manner, particularly during the acute phase of illness, are essential for successful therapeutic outcomes.

Despite the “concentration-dependent” bactericidal activity, the pharmacokinetic and pharmacodynamic (PK/PD) target of gentamicin therapy remains inconclusive in critically ill patients. The maximum gentamicin plasma concentration (C_{\max}) to the minimum inhibitory concentration (MIC) ratio from 8–10 is advocated to justify the prediction of efficacy in critically ill patients for treatment of infections.^{4,5} However, *in vivo* study reported that the 24-hour area under the concentration-time curve to MIC (AUC_{24h}/MIC) ratio around 30–50 was associated with bacteriostasis, and the ratios around 80–100 were associated with 1 and 2 \log_{10} bacterial reduction, respectively.^{3,6} In addition, the AUC_{24h}/MIC ratio ≥ 110 significantly improved the clinical cure in patients with serious Gram-negative bacterial infections.^{7,8} As a result, the AUC_{24h}/MIC ratio ≥ 110 has recently been proposed as an appropriate PK/PD target for severe infection.^{6–9} From a safety perspective, $AUC_{24h} > 700$ mg·h/L and the minimum gentamicin plasma concentration (C_{\min}) > 2 mg/L are also suggested as the indicator for nephrotoxicity.^{9,10} To date, no studies have evaluated the achievement of gentamicin both for PK/PD targets for efficacy (C_{\max}/MIC and AUC_{24h}/MIC ratios) and risk of nephrotoxicity (AUC_{24h} and C_{\min}) in critically ill patients. The purpose of this is to define optimal once-daily gentamicin dosing regimens for efficacy and safety in critically ill patients during an acute illness (first 72 hours of infection).

Materials and Methods

Search Strategy, Study Selection and Data Extraction

The following Medical Subject Heading (MeSH) terms: “gentamicin”, “pharmacokinetics”, “critically ill”, “intensive care” and synonymous words were used to search in PubMed, EMBASE, SCOPUS, CINAHL and EBSCO. All original publications of gentamicin traditional pharmacokinetic studies in humans and in English that entered the databases by September 2022 were included. The searched studies were focused to extract individual or study-based pharmacokinetics data with mean and standard deviation. In addition, we also conducted a review on online available secondary references and included these if eligible. Two investigators (AMY and TD) independently found and evaluated studies for potential inclusion and exclusion.

Pharmacokinetic Model Development/Mathematical Pharmacokinetic Models

The traditional gentamicin pharmacokinetic studies in critically ill adult patients were included for evaluation. The studies were excluded if they included pregnant women, patients receiving extracorporeal membrane oxygenation, or renal replacement therapy. All selected published articles based on inclusion and exclusion criteria have undergone extensive scrutiny to gather the required pharmacokinetic parameters of gentamicin to generate the time versus concentration profiles (Figure S1). Data extracted from the selected publications of gentamicin pharmacokinetic parameters (V_d , CL , Ke) and total body weight were combined to calculate mean and standard deviation. In addition, the upper and lower range of each parameter were extracted and used in the MCS.

Furthermore, in a clinical setting gentamicin concentration best fit with the one-compartment pharmacokinetic model.⁵ Hence, in this study, a one-compartment model with first-order elimination was developed to predict gentamicin concentration for 72 hours of the initial antibiotic therapy. The gentamicin dosage was calculated based on total body weight. The equation used in the model to calculate gentamicin plasma concentrations in individual virtual patients is shown in equation 1. The AUC_{24h} for each day was calculated by using the trapezoidal formula for each virtual individual.

$$C(t) = \frac{D * TBW}{CL * T} \times (1 - e^{-Ke * t}) \times e^{-Ke * (T - t)} \quad (1)$$

Where D = gentamicin dose (mg/kg), TBW = total body weight (kg), Ke = elimination rate constant, t = infusion time (0.5 hour); T = dosing interval (24 hours), and CL = Clearance.

Monte Carlo Simulations

The mean, standard deviation (SD), upper and lower PK parameters for gentamicin obtained from the selected studies were used to build 10,000 virtual patients using the Crystal Ball, Oracle software.¹¹ Since the targeted population in the simulation was adults, total body weight (kg) was set at the range 40 to infinity in MCS analysis. Gentamicin plasma

concentration versus time profiles from 0–72 hours were generated which were divided into first (0–24 h), second (24–48 h), and third day (48–72 h). The processes mentioned in the above section were repeated to assess the various doses regimen ranging from 5–10 mg/kg once-daily gentamicin.

Probability of Target Attainment Prediction

The probability of target attainment (PTA) was estimated employing PK/PD targets for efficacy, i.e., AUC_{24h}/MIC , and C_{max}/MIC with a set of distinctive MIC values. The gentamicin dosing efficacy and risk of nephrotoxicity were assessed for the first and third day by considering $C_{min} > 2$ mg/L and $AUC_{24h} > 700$ mg·h/L.^{10,12} The optimal gentamicin dose recommended for critically ill patients was defined as the dose that achieves at least 90% of the efficacy target with the minimum risk of nephrotoxicity. MICs were set at 0.5, 1, 2, and 4 mg/L, representing a variety of susceptible pathogen inhibitions as determined by the United States Committee on Antimicrobial Susceptibility Testing (USCAST).¹³

Results

Gentamicin pharmacokinetic parameters selected from 21 studies were gathered for the simulation (Table S1).^{14–34} This included critically ill patients admitted to medical, surgical, and traumatic care units. Among a total of 1215 patients, 90.5% of were confirmed for severe infections. Seven studies reported gentamicin PK parameters from the first dose, for which plasma levels during the acute phase (within 48–72 hours) were retrieved. Steady state PK parameters were obtained from another 2 studies. The pooled values (mean \pm SD) of V_d , CL, and K_e of gentamicin during the acute phase were 0.33 ± 0.20 L/kg, 4.70 ± 2.89 L/h, and 0.18 ± 0.10 h⁻¹, respectively. Total body weight (70.8 ± 19.9 kg) was used as dosing weight in these critically ill patients. Additional parameters used in the model are presented in Table S2.

The PTAs for the gentamicin efficacy in severe infection ($AUC_{24h}/MIC \geq 110$) are shown in Table 1. Based on $AUC_{24h}/MIC \geq 110$, no gentamicin regimens were sufficient to produce the optimal efficacy in critically ill patients for $MIC \geq 1$ mg/L. Gentamicin 7 mg/kg/day was adequate for $MIC \leq 0.5$ mg/L. Figure 1 presents the PTAs for various

Table 1 Probability of Target Attainment (% PTA) for Gentamicin Regimens Achieving $AUC_{24h}/MIC \geq 110$ for MIC of 0.5, 1, 2, and 4 mg/L on Day 1 and Day 3 of Therapy in Critically Ill Patients

Dose, mg/kg/day (Mean \pm SD)	Day of Therapy	% PTA Target of $AUC_{24h}/MIC \geq 110$			
		MIC 0.5 mg/L	MIC 1 mg/L	MIC 2 mg/L	MIC 4 mg/L
5 (368.2 \pm 87.9)	1	77.3	34.7	6.3	0.4
	3	80.2	38.2	7.4	0.4
6 (440.7 \pm 107.2)	1	85.4	46.5	11.1	0.9
	3	87.7	50.0	12.8	1.0
7 (513.9 \pm 123.6)	1	90.9	55.8	16.4	1.8
	3	92.6	59.5	18.5	2.1
8 (586.0 \pm 143.0)	1	94.3	64.8	22.0	3.0
	3	95.5	68.3	24.9	3.7
9 (660.8 \pm 158.6)	1	96.8	71.6	28.7	4.7
	3	97.9	75.0	31.8	5.4
10 (732.9 \pm 176.9)	1	98.0	77.7	34.8	6.3
	3	98.6	80.7	38.1	7.6

Note: Data are presented as the percentage (%) and the mean \pm standard deviation (SD) in parentheses.

Abbreviations: AUC_{24h}/MIC , a ratio of the 24-hour area under the concentration-time curve (AUC_{24h}) to minimum inhibitory concentration (MIC) ratio; % PTA, percentage of probability target attainment.

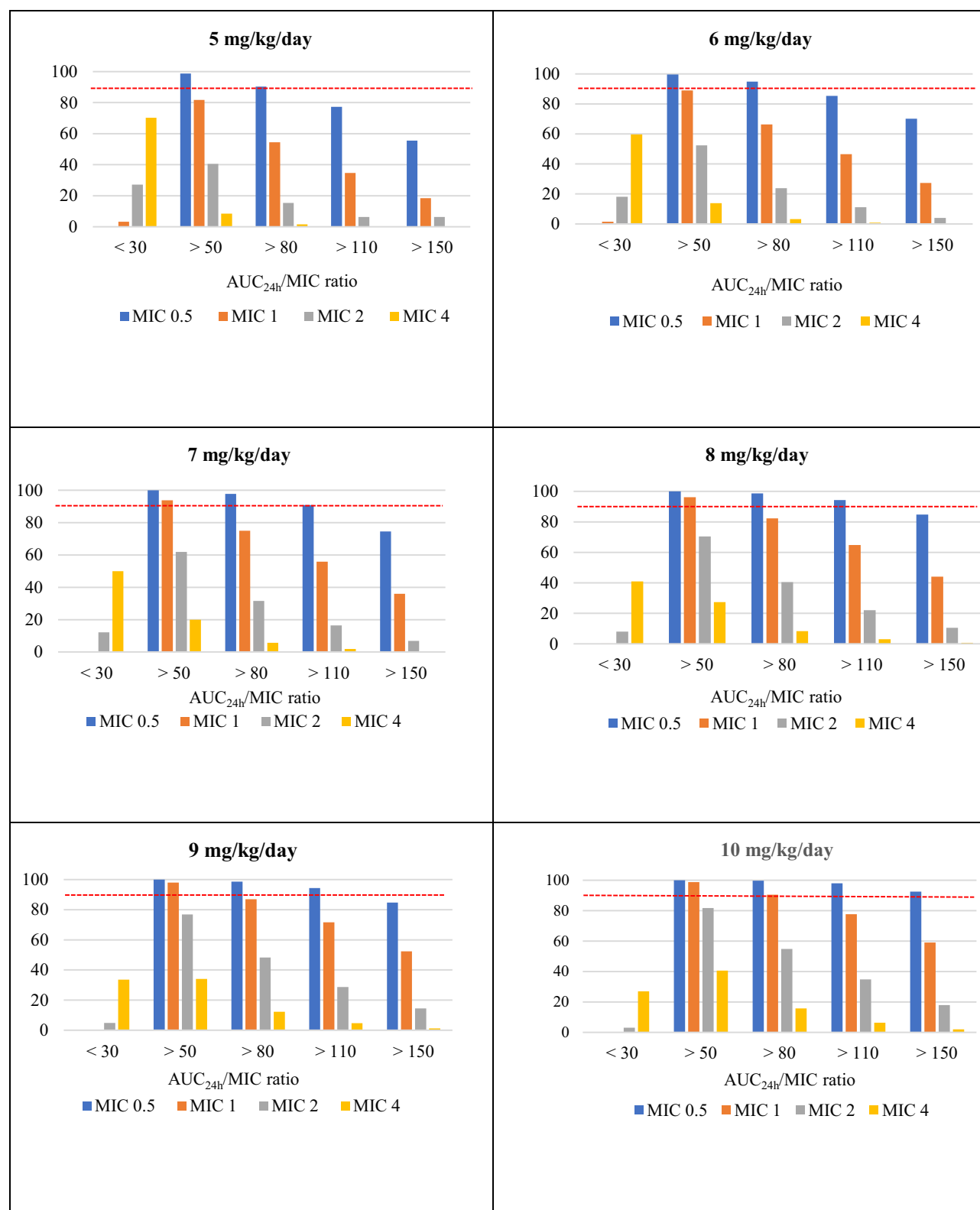


Figure 1 Distribution of achieving various AUC_{24h}/MIC ratio using gentamicin regimens ranging from 5–10 mg/kg/day in critically ill patients. The dashed red line represents the optimal doses which achieved at least 90% of the probability of target attainment (PTA).

Table 2 Probability of Target Attainment (% PTA) for Gentamicin Regimens Achieving C_{\max}/MIC Ratio of ≥ 8 , and ≥ 10 for MIC of 0.5, 1, 2, and 4 Mg/L on Day 1 of Therapy in Critically Ill Patients

Dose (mg/kg/day)	MIC 0.5 mg/L		MIC 1 mg/L		MIC 2 mg/L		MIC 4 mg/L	
	≥ 8	≥ 10	≥ 8	≥ 10	≥ 8	≥ 10	≥ 8	≥ 10
5	95.2	91.2	76.4	66.3	41.2	30.6	13.2	8.2
6	97.5	95.0	83.1	75.6	51.5	39.9	19.4	12.5
7	98.7	96.9	88.0	80.5	59.3	47.5	25.5	17.6
8	99.1	97.8	91.2	85.5	66.4	55.3	31.3	21.5
9	99.6	98.7	93.4	88.4	72.2	61.5	37.6	27.0
10	99.7	99.1	95.0	91.2	76.2	66.9	42.5	31.8

Note: Data are presented as the percentage (%) and the mean \pm standard deviation (SD) in parentheses.

Abbreviations: C_{\max}/MIC , a ratio of maximum concentration of drug to minimum inhibitory concentration (MIC) ratio; % PTA, percentage of probability target attainment.

Table 3 The Probability of Developing Nephrotoxicity Predicted by $AUC_{24h} > 700$ mg·h/L and $C_{\min} > 2$ mg/L on Day 1 and Day 3 of Gentamicin Therapy in Critically Ill Patients

Dose (mg/kg/day)	$AUC_{24h} > 700$ mg h/L (%)		$C_{\min} > 2$ mg/L (%)	
	Day 1	Day 3	Day 1	Day 3
5.0	0.10	0.11	3.9	5.5
6.0	0.10	0.13	5.7	8.0
7.0	0.21	0.25	8.0	10.4
8.0	0.43	0.46	10.8	13.2
9.0	0.72	0.78	13.0	15.5
10.0	1.10	1.29	15.9	18.4

Notes: Data are presented as the percentage (%) and the mean \pm standard deviation (SD) in parentheses.

Abbreviations: AUC_{24h} , area under the curve for 24 hours; C_{\min} , a trough concentration.

AUC_{24h}/MIC targets. Gentamicin 5 and 7 mg/kg/day were the optimal doses for achieving the bacteriostatic (target $AUC_{24h}/MIC > 50$) for MIC 0.5 and 1 mg/L, respectively.

For the pathogens with MIC of 0.5 mg/L, the optimal gentamicin dose using $C_{\max}/MIC \geq 8$ and ≥ 10 was 5 mg/kg/day. However, when MIC increased to 1 mg/L, the optimal gentamicin doses were 8 and 10 mg/kg/day for the target $C_{\max}/MIC \geq 8$ and ≥ 10 , respectively (see Table 2). No gentamicin regimens were sufficient to produce the optimal target of C_{\max}/MIC in critically ill patients when $MIC \geq 2$ mg/L.

Table 3 presents the risk of nephrotoxicity, focusing on either $AUC_{24h} > 700$ mg·h/L, or $C_{\min} > 2$ mg/L. In this study, the probability of developing nephrotoxicity depended on gentamicin dose and duration of therapy. Higher incidence of nephrotoxicity was recorded with criteria of minimum plasma gentamicin level ($C_{\min} > 2$ mg/L), compared with the $AUC_{24h} > 700$ mg·h/L.

Discussion

Gentamicin is known for its concentration-dependent activity and can be predicted by C_{\max} and C_{\min} for the efficacy and risk of nephrotoxicity or ototoxicity. Hence once-daily dosing is more favorable for clinical practice. During therapeutic

drug monitoring, individualized therapy using a Bayesian prediction method avoids the problem of inter- or intra-patient variability (IIV) in patients. IIV leads to low or high gentamicin exposure in clinical settings. Therefore, physicians and clinical pharmacists are always working together to improve the effectiveness and reduce the risk of once-daily gentamicin dosing in hospitals throughout the world.^{9,10,12} Our study employs the MCS method to create virtual populations of critically ill patients. This method was examined for various “what if” scenarios for optimal dosing and risk of nephrotoxicity. This technique generates PK/PD data to assess antibacterial dosing regimens and determine PTA. Previously, several studies have used the MCS to establish optimal antibiotic doses for vulnerable patients, proving its efficacy.^{35–37} Gathered published pharmacokinetic parameters showed enhanced Vd and fluctuation of clearance due to aggressive fluid resuscitation, vasodilation and capillary leakage, systematic inflammatory response syndrome in acute sepsis. Changes in the Vd (range from 0.27–0.83 L/kg) parameter have been reported in critically ill patients admitted in intensive care units.³⁸ To date, PK/PD targets for gentamicin mostly depend on the plasma concentration and severity of the infection.⁵ In vitro studies data suggest that C_{\max}/MIC ~8–10 is sufficient for all pathogens, even *Enterobacteriaceae*.³⁹ In clinical settings, C_{\max}/MIC ratio ~8–10 predicts a cure rate of 90% in Gram-negative infected patients.^{40,41} A more aggressive PK/PD target of $C_{\max}/\text{MIC} \geq 10$ should be considered in infections caused by the high burden resistant pathogens.^{42,43} The $\text{AUC}_{24\text{h}}/\text{MIC}$ was also reported to be a good predictor of the efficacy in ODDG.^{6,9}

In vivo study proved that there is 1–2 \log_{10} of killing for *K. pneumonia* when $\text{AUC}_{24\text{h}}/\text{MIC}$ ~80 and 100, respectively.^{3,6,39} Smith et al⁸ reported that the $\text{AUC}_{24\text{h}}/\text{MIC}$ ratio ≥ 110 significantly improved the clinical cure in patients with serious Gram-negative bacterial infections. Higher $\text{AUC}_{24\text{h}}/\text{MIC}$ of ≥ 150 and ≥ 175 of gentamicin monotherapy was also associated with fever and leukocytosis resolution in sepsis patients, respectively.⁴⁰ Therefore, in this study, we utilized both C_{\max}/MIC and $\text{AUC}_{24\text{h}}/\text{MIC}$ for predicting the efficacy of gentamicin in critically ill patients.

For the highly susceptible pathogens with $\text{MIC} \leq 0.5$ mg/L, our study revealed that gentamicin 5 mg/kg/day was the optimal dose with $C_{\max}/\text{MIC} \geq 8$ –10. When the MIC increased to 1 mg/L, a recommended dose should be 8 mg/kg/day to attain PTA. However, for pathogens with MIC of 2 mg/L, no studied dose achieved the optimal target ($>90\%$ PTA). Even with the maximum studied dose of 10 mg/kg/day, the target attainment for C_{\max}/MIC of 8 or 10 remained lower than 80% (76.2% and 66.9%, respectively). In similar fashion Gonçalves-Pereira et al⁴⁴ reported that 65.5% of critically ill patients receiving gentamicin 7.4 mg/kg/day were able to reach the target C_{\max}/MIC of 8 for the treatment of bacterial infections with MIC of 2 mg/L. Rea et al⁴⁵ also reported that a gentamicin dosing regimen of 7 mg/kg in critically ill patients is inadequate and only fulfills 20% of the $C_{\max}/\text{MIC} > 10$ for MIC of 2 mg/L.

Our simulation showed that when the MIC is 1 mg/L, the optimal gentamicin dose is 8 mg/kg/day to achieve the C_{\max}/MIC target >8 . However, gentamicin 10 mg/kg/day should be considered if the target C_{\max}/MIC is >10 . The French guideline also recommended a maximum gentamicin dose of 8 mg/kg/day for general critically ill and surgical patients with trauma, if the MIC is not more than 0.5 mg/L.⁴⁶ However, Allou et al⁴⁷ reported only 30% of ICU patients reached a C_{\max} of ≥ 16 mg/L with gentamicin 8 mg/kg/day. The study in critically ill patients with severe sepsis also achieved a C_{\max} target of ≥ 30 mg/L in 59% of patients on the first day of therapy.⁴⁸

While the C_{\max}/MIC target is commonly used in clinical practice due to its simplicity, Roger et al⁴⁹ provided strong evidence that the $C_{\max}/\text{MIC} > 8$ is not a reliable indicator of PK/PD target attainment and clinical outcomes based on efficacy and multivariable analysis. $\text{AUC}_{24\text{h}}/\text{MIC}$ has the advantage of representing cumulative exposure throughout the dosing period and being less affected by variations in sampling times for drug concentration.⁴⁹ The optimal $\text{AUC}_{24\text{h}}/\text{MIC}$ target may vary depending on the severity of the infection and the patient population, ranging from 30–50 for non-critically ill patients with lower and uncomplicated urinary tract infections (UTIs) or those receiving combination therapy to 80–100 for critically ill patients with non-UTI infections or those receiving gentamicin monotherapy.^{3,6} He et al⁵⁰ proposed using an $\text{AUC}_{24\text{h}}/\text{MIC} \geq 100$ to guide gentamicin dosing in critically ill patients, particularly for infections with $\text{MIC} \leq 1$ mg/L. They suggested a starting gentamicin dose of 7 mg/kg/day.⁵⁰

In vivo study revealed that the $\text{AUC}_{24\text{h}}/\text{MIC}$ ~30–50 was associated with bacteriostasis; therefore, the $\text{AUC}_{24\text{h}}/\text{MIC}$ ratio >50 should be adequate for prevention of infections, especially in surgical or trauma injury patients.⁶ These patients commonly received gentamicin in combination with cephalosporins and adequate wound irrigation and debridement for prevention of skin and soft tissue infection.⁵¹ In our study, when the MIC was <1 mg/L, the lowest gentamicin dose that attained the $\text{AUC}_{24\text{h}}/\text{MIC} > 50$ for more than 90% was 7 mg/kg/day. Similarly, the USCAST¹³ recommended a dose of

7 mg/kg/day, which achieved a high PTA (99.8% and 89.5%) with an $AUC_{24h}/MIC \geq 30.7$ based on MIC values of 1 and 2 mg/L, respectively. However, higher AUC_{24h}/MIC targets of ≥ 80.3 resulted in lower PTA, 58.8% and 2.1% for MIC values of 1 and 2 mg/L, respectively.¹³

The AUC_{24h}/MIC ratio ≥ 110 is currently accepted to be beneficial for treating severe or serious infections.⁸ Our study revealed that the optimal gentamicin dose for the $AUC_{24h}/MIC \geq 110$ target was 7 mg/kg/day for pathogens with $MIC \leq 0.5$ mg/L. However, when the MIC increased to 1 mg/L, approximately 56% of patients reached this target with the dose of 7 mg/kg/day. After increasing the gentamicin dose to 10 mg/kg/day, the AUC_{24h}/MIC target stayed around 80%. The gentamicin dose of 10 mg/kg/day was the only regimen that achieved >90% target of $AUC_{24h}/MIC \geq 150$ for pathogens with $MIC \leq 0.5$ mg/L, but it simultaneously increased the risk of nephrotoxicity. Therefore, gentamicin should not be recommended as monotherapy for pathogens with $MIC > 2$ mg/L when considering $AUC_{24h}/MIC > 110$ in critically ill patients.

Previous studies reported that the risk of gentamicin-induced nephrotoxicity depended on dose, long term use, and concurrent administration of other nephrotoxic agents. It was also provoked by alteration in pathophysiological conditions of individual patients.^{52,53} Nicolau et al⁵⁴ found that out of 2184 patients, only 1.2% of patients experienced nephrotoxicity (rise in serum creatinine of >0.5 mg/L) after a median duration of 7 days of therapy. The risk of nephrotoxicity is significantly lower when $C_{min} < 2$ mg/L.¹⁰ However, $C_{min} < 1$ mg/L was recommended in clinical practice to minimize nephrotoxicity.⁹ The $AUC_{24h} > 700$ mg·h/L was also a good predictor of nephrotoxicity in patients receiving gentamicin once-daily dosing for at least 72 hours.¹² However, in this study, we selected two parameters i.e., $AUC_{24h} > 700$ mg·h/L or $C_{min} > 2$ mg/L to predict gentamicin-induced nephrotoxicity. Using the target of $AUC_{24h} > 700$ mg·h/L, we found a minimal risk of nephrotoxicity. Our simulation revealed the $C_{min} > 1$ mg/L ranged from 19–37.9% after three days of gentamicin 5–10 mg/kg/day therapy in critically ill patients. For $C_{min} > 2$ mg/L, the risk of nephrotoxicity ranged from 5.5–18.4% for 5–10 mg/kg/day of gentamicin dosing regimen on day 3. Therefore, gentamicin once-daily dosing for short duration (for 3 days) showed a minimal risk of nephrotoxicity. Routine monitoring of plasma gentamicin concentrations for nephrotoxicity may not be necessary within the first 3 days after gentamicin initiation.

Gentamicin dosing should be based on epidemiological or geographic antimicrobial susceptibility testing and clinical effectiveness on various MICs.^{55–57} Considering both efficacy targets of $C_{max}/MIC \sim 8–10$ and $AUC_{24h}/MIC \geq 110$ and the risk of nephrotoxicity, the optimal gentamicin dose of 8 mg/kg/day would be sufficient to initiate therapy in critically ill patients. More than 90% of critically ill patients receiving this dose could achieve both targets for treating pathogens with $MIC < 0.5$ mg/L. For pathogens with MIC of 1 mg/L, the %PTA after 3 days of therapy ranged between ~70–90%. Our gentamicin dosing recommendation of 8 mg/kg/day is consistent with the recommendation by the French guideline.⁴⁷ However, gentamicin monotherapy should not be recommended for the treatment of pathogens with $MIC \geq 2$ mg/L.

To our knowledge, this is the first study employing both AUC_{24h}/MIC and C_{max}/MIC ratios, as the targets for efficacy of gentamicin in critically ill patients. In this study, we focused on the acute phase of illness, i.e., within 3 days of gentamicin initiation, where the culture and sensitivity results would be available thereafter. If the culture results reveal pathogens with the MIC of gentamicin > 2 mg/L, then alternative antibiotics or gentamicin use in combination with other antibiotics should be initiated to manage the infection. There is a lack of consensus in the scientific community regarding a single PK/PD target for both efficacy and nephrotoxicity. Bland et al⁶ have already emphasized the significance of utilizing accurate and effective PK/PD targets. Gentamicin continues to be widely used as an empirical antibiotic and resistance patterns are also changing drastically in significance. Hence, particularly in tropical countries, there is a need for optimal dosing information. This study serves as a valuable resource and guidance for clinicians.

There are a few limitations to this study. First, we gathered the pharmacokinetic data from 21 earlier published studies representing critically ill patients; therefore, inter- or intra-patient variability in pathophysiological conditions could not be excluded in a heterogeneous population. Second, total body weight was used for the prediction; therefore, the recommended optimal gentamicin doses cannot be applicable to the ideal body weight or adjusted body weight for dosing. Third, our result may not apply if the patient has significant changes in pharmacokinetic parameters within the first 72 hours. Our study predicted gentamicin concentrations based on the pharmacokinetic parameters during the acute phase of illness. If clinicians plan to continue treatment for more than 3 days, efficacy and toxicity should be closely monitored.

Conclusion

This is the first study targeting both AUC_{24h}/MIC and C_{max}/MIC ratios as targets for efficacy of gentamicin in critically ill patients. The initial gentamicin dose of 8 mg/kg/day was adequate for empirical or documented therapy against a susceptible pathogen, $MIC < 1$ mg/L since it showed both efficacy targets with minimum risk of nephrotoxicity. However, for a documented therapy against a pathogen with $MIC \geq 2$ mg/L, gentamicin monotherapy should not be recommended. While using gentamicin, clinicians should be cautious and maintain close monitoring for therapeutic outcomes and risk of nephrotoxicity. Furthermore, clinical studies are essential to confirm our recommendation.

Abbreviations

AUC_{24h} , 24-hour area under the concentration-time curve; C_{max} , maximum gentamicin plasma concentration; C_{min} , minimum gentamicin plasma concentration; CL, clearance; K_e , elimination rate constant; IIV, inter- or intra-patient variability; ODDG, once-daily dosing of gentamicin; MCS, Monte Carlo simulation; MIC, minimum inhibitory concentration; PD, pharmacodynamic; PK, pharmacokinetic; PTA, probability of target attainment; USCAST, The United States Committee on Antimicrobial Susceptibility Testing; V_d , volume of distribution.

Data Sharing Statement

The datasets utilized and analyzed in this research are accessible from the corresponding authors upon request in the future without any specific rationale.

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Disclosure

The authors declare that they have no conflicts of interest in this work.

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