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Reappraisal of Contemporary Pharmacokinetic and Pharmacodynamic Principles for Informing Aminoglycoside Dosing

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Conflicts of interest

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Abstract

Therapeutic drug management is regularly performed for aminoglycosides in an effort to maximize their effectiveness and safety. The ratio of maximum plasma drug concentration to minimum inhibitory concentration (C_{max}/MIC) has long been regarded as the primary pharmacokinetic/pharmacodynamic (PK/PD) index of clinical efficacy for aminoglycosides due to their concentration-dependent killing. In this review, however, we discuss why the area under the plasma concentration–time curve (AUC)/MIC ratio may be a more reliable indicator of bacterial killing and clinical efficacy for these agents. The definitive AUC/MIC efficacy targets for aminoglycosides are less clear, unlike those that exist for fluoroquinolones. Evaluation of available literature suggests that an AUC/MIC ratio of 30–50 for aminoglycoside therapy may provide optimal outcomes when targeting non–critically ill immunocompetent patients with low–bacterial burden gram-negative infections such as urinary tract infections, or in patients receiving additional gram-negative therapy with good source control. However, an AUC/MIC target of 80–100 may be more prudent when treating patients with aminoglycoside monotherapy or in critically ill patients with high–bacterial burden infections, such as nosocomial pneumonia. Reappraisal of current antimicrobial susceptibility breakpoints for aminoglycosides against gram-negative bacteria may also be necessary to achieve these AUC/MIC targets and ensure that current empiric doses are not grossly suboptimal in critically ill patients. Although it has been historically difficult to calculate AUCs in clinical practice, equation-based and Bayesian approaches now can be used to estimate the AUC in clinical practice, with limited PK sampling. Additional research is needed to better define optimal AUC/MIC targets for efficacy, especially when drugs are used in combination, as well as PK/PD targets associated with suppression of resistance. It is also important to determine if AUC can predict nephrotoxicity of these agents or whether trough concentrations should be used instead.

Key words: aminoglycosides, therapeutic drug management, critical illness, pharmacokinetics, pharmacodynamics, PK/PD, AUC/MIC

Introduction

Aminoglycosides are natural antibiotics produced by soil bacteria that were first introduced for clinical use in the 1940s as streptomycin and neomycin.[1] Over the intervening years, several other natural and semisynthetic aminoglycosides have been developed including kanamycin (1957), gentamicin (1963), tobramycin (1967), amikacin (1976; a semisynthetic derived from kanamycin), and plazomicin (2018; a semisynthetic derived from sisomicin). Four compounds—amikacin, gentamicin, tobramycin, and plazomicin—are currently approved by the United States Food and Drug Administration (FDA) for the treatment of serious infections due to gram-negative or gram-positive bacteria.[2-5] Aminoglycosides are active in vitro against both gram-positive and gram-negative pathogens, but for many infections, they are primarily recommended for use in combination therapy. Table 1 provides the United States guideline recommendations for the use of legacy aminoglycosides (gentamicin, tobramycin, and amikacin) to treat severe Infections.[6-10]

Amid concerns about toxicity (particularly irreversible vestibular injury), the use of aminoglycosides began to decline in the 1980s in favor of newer antibiotic classes such as fluoroquinolones, which were perceived to be less toxic.[1] However, the increasing prevalence of multidrug-resistant (MDR) gram-negative pathogens—including carbapenem-resistant *Enterobacteriaceae, Pseudomonas aeruginosa*, and *Acinetobacter* spp., for which therapeutic options are limited—has led to renewed interest in aminoglycosides for use as monotherapy or typically in combination with other antibacterials.[11,12] Given the reemergence of aminoglycosides as an important treatment option for infections caused by MDR gram-negative bacteria, an improved understanding is needed of the pharmacokinetic/pharmacodynamic (PK/PD) profile and therapeutic targets of these agents. Historically, the ratio of maximum plasma drug concentration to minimum inhibitory concentration (C_{max}/MIC) has been considered the PK/PD index most closely linked to bacterial killing and clinical efficacy for aminoglycosides.[13] However, support is now increasing for the area under the plasma concentration–time curve (AUC)/MIC ratio as a more accurate measure of exposure-efficacy relationships.[14] In this review, we discuss our updated understanding of the PK/PD profile of aminoglycosides and review the data supporting the shift from C_{max}/MIC to AUC/MIC as the better index

for efficacy. We further describe how the AUC can be adopted to guide aminoglycoside dosing in clinical practice. Finally, we suggest future directions for research on the PK/PD properties of aminoglycosides.

Support for the C_{max}/MIC Ratio as a PK/PD Index

Data from in vitro pharmacodynamic infection models and animal studies conducted in the 1980s highlighted the importance of the C_{max}/MIC ratio and showed that once-daily aminoglycoside dosing regimens, in large, had similar efficacy to multiple-daily dosing regimens.[15-19] Although some early animal studies in neutropenic rodents showed less efficacy with once-daily dosing compared with multiple-daily dosing, it is important to note that dosing was not humanized in these studies, and the differences in response rates were postulated as due to the more rapid elimination of aminoglycosides in rodents relative to humans.[20,21] Best early clinical support for C_{max}/MIC as the appropriate PK/PD index for aminoglycoside dosing was provided in a 1987 landmark study by Moore and colleagues.[22] This study included data from four earlier clinical trials of gentamicin 2 mg/kg every 8 hours, tobramycin 2 mg/kg every 8 hours, and amikacin 8 mg/kg every 8 hours, and examined the association between C_{max} and clinical response. Plasma samples were taken 1 hour prior to (trough) or 1 hour after (peak) a 30-minute infusion, and maintenance doses were adjusted to achieve a C_{max} of 5–10 mcg/ml for gentamicin and tobramycin, and 20–40 mcg/ml for amikacin. In total, 236 patients treated with aminoglycosides for suspected sepsis caused by gram-negative pathogens were included in this pooled analysis. The urinary tract and lower respiratory tract were the most common sites of infection (64% and 16%, respectively), and 37% of patients had bacteremia. Overall, clinical response was observed in 80% of patients, and the maximal (highest value during therapy) C_{max}/MIC ratio was strongly associated with clinical response after adjustment for underlying severity of illness and other factors correlated with response. More important, a graded exposure response was observed with clinical responses of approximately 70%, 84%, 88%, and 92% when the maximal C_{max}/MIC ratios were 4 to < 6, 6 to< 8, 8 to < 10, and ≥ 10, respectively.

Kashuba and colleagues also highlighted the therapeutic importance of the first measured C_{max}/MIC in their evaluation of 78 patients with nosocomial pneumonia due to gram-negative bacteria who were treated with high-dose, extended-interval gentamicin or tobramycin.[23] In this study, attainment of a C_{max}/MIC ratio of ≥ 10 was associated with a 90% probability of temperature and white blood cell count resolution by day 7 of therapy. The AUC/MIC ratio was also found to be predictive of microbiologic response (AUC from time zero to 24 hours [$AUC_{0–24}$]/MIC ratio ≥ 150 was associated with a

90% probability of temperature resolution, and a ratio of ≥ 175 was associated with a 90% probability of white blood cell count resolution), but statistical analyses showed that the C_{max}/MIC ratio was the most important predictor of clinical and microbiologic resolution. Although a correlation between the C_{max}/MIC and AUC/MIC ratios was not reported, it was assumed to be high given that both PK/PD parameters reflect concentration-dependent activity.

Combined, these studies have contributed to the pharmacologic rationale for high-dose, extended-interval dosing for patients with gram-negative infections. Although they highlight the benefits of achieving a high C_{max}/MIC ratio, these studies were not prospectively designed to ascertain the optimal PK/PD index. For example, whereas the patients included in the analysis by Moore et al. received traditional or multiple daily doses of aminoglycosides,[22] most institutions now use once-daily or high-dose, extended-interval dosing for patients with gram-negative infections. Furthermore, this study only evaluated one dosing regimen, making it even more difficult to elucidate the key PK/PD efficacy driver.

Support for the AUC/MIC Ratio as a PK/PD Index

Although the prevailing wisdom has historically been that the C_{max}/MIC ratio is the critical exposure target for aminoglycosides, an equivalent body of evidence suggests that the AUC/MIC ratio is the PK/PD driver for bacterial killing and efficacy. When attempting to identify the PK/PD index for an antibiotic, it is preferable to conduct in vivo or dynamic in vitro PK/PD preclinical model studies rather than clinical studies, which have a number of disadvantages for the reasons mentioned earlier. One way to separate the collinearity of these measures and identify the PK/PD measure most closely associated with efficacy is through the use of dose-escalation and dose-fractionation studies in preclinical PK/PD infection models. As stated above, dose-fractionation studies in animals and in vitro PK/PD infection models have not demonstrated differences in efficacy between once-daily, multiple-daily, and continuous-infusion aminoglycoside dosing regimens,[15-19] indicating that the PK/PD driver for efficacy is better linked to the AUC/MIC ratio than the C_{max}/MIC ratio. If the C_{max}/MIC ratio was more important than the AUC/MIC ratio, then the once-daily regimens would have better efficacy than the multiple-daily dosing regimens. The best illustrative example that highlights that the AUC/MIC ratio is the preferred PK/PD efficacy driver for aminoglycosides comes from a murine neutropenic thigh model of infection with *Klebsiella pneumoniae* by Craig et al.[13] In this extensive in vivo investigation that sought to elucidate the PK/PD target for amikacin, the authors found that the $AUC_{0–24}$/MIC ratio was more strongly

correlated (R^2=96%) with efficacy (measured by change in colony-forming units [CFU])/g from baseline) than the C_{max}/MIC ratio (R^2=84%; Figure 1).[13] Furthermore, as part of 2016 report from the National Antimicrobial Susceptibility Testing Committee for the United States (USCAST), data from previous neutropenic mouse thigh and lung infections models for gentamicin, tobramycin, and amikacin were pooled, and subsequent analyses demonstrated nearly identical relationships between total drug plasma $AUC_{0–24}$/MIC ratio and change in the bacterial density of *Enterobacteriaceae* after 24 hours of therapy for all included aminoglycosides.[14] Similarly, animal and in vitro models have demonstrated that the AUC/MIC ratio is the index that correlates best with efficacy for plazomicin.[24-26]

The clinical predictive value of the AUC/MIC ratio is supported in studies by Smith et al. and Mouton et al.[27,28] In a study of 23 patients receiving tobramycin monotherapy for intraabdominal or lower respiratory tract infections due to gram-negative pathogens, an $AUC_{0–24}$/MIC ratio ≥ 110 was associated with a significantly higher rate of clinical cure (80% vs 47% for an $AUC_{0–24}$/MIC ratio < 110, p<0.01).[27] Among 13 patients with cystic fibrosis aged 21 years or younger receiving tobramycin in combination with ticarcillin for management of *P. aeruginosa* infection,[28] the ratio of *f*AUC (AUC corrected for protein binding) to MIC was significantly correlated (r=0.77, p=0.002) with improvement in forced expiratory volume (FEV_1). The correlation between *f*peak/MIC and FEV_1 was also significant (r=0.67, p=0.002). The maximum effect was achieved at an *f*AUC/MIC ratio of around 50 and an *f*peak/MIC ratio of around 5.[28]

Practical Considerations for Favoring AUC/MIC Ratio as a PK/PD Index

Although past evidence illustrates that the C_{max}/MIC and AUC/MIC ratios are each predictive of clinical outcomes and microbiologic eradication, practical concerns provide reasons to prefer the AUC/MIC ratio as the PK/PD index to guide dosing of aminoglycosides**.** Estimates of C_{max} in a single patient can vary substantially based on the duration of the infusion and the timing of C_{max} sample collection after start of dosing, impairing the reliability of this measure. Recommendations and reported practices for obtaining the C_{max} measure have ranged from a blood sample collected immediately to 30, 60, or even 120 minutes after a bolus or a 30-, 60-, or 120-minute intravenous infusion.[22,29-32] A survey of intensive care units highlighted the continuing variability in administering aminoglycosides and collecting C_{max} concentrations.[33] In this study, the median duration of intravenous infusion was 60 minutes for amikacin versus 30 minutes for gentamicin. Timing of C_{max} concentration collection was also found to vary considerably across centers.[33]

The consequences of sampling the C_{max} concentrations at different times after start of dosing were highlighted in the study by Blaser et al.[32] In this study, serum concentrations of gentamicin, amikacin, and netilmicin from 58 patients were measured immediately after a 30-minute infusion and then 90 minutes later (2-hour values). The mean ratios of the 30-minute to 2-hour concentrations were 2.21 for gentamicin, 2.12 for amikacin, and 2.18 for netilmicin. Thus, a serum concentration measured 30 minutes after dosing was more than twice as high as one measured 2 hours after dosing. Similarly, Demczar and colleagues demonstrated that the distribution phase of aminoglycosides can last between 1.45 and 2.7 hours after the start of the infusion, depending on the dose infused, and the C_{max} can vary considerably depending on when the blood sample is collected (30, 60, or 120 minutes) in relationship to the dose.[34] Furthermore, they indicated that sampling during the distribution phase can severely overestimate the C_{max}. Thus, the potentially large differences in observed concentrations measured over the first 2 hours after drug infusion reflect the difficulty in relying on C_{max} as an accurate measure of an aminoglycoside's PK/PD profile in a single patient.

In contrast to the intrapatient variability associated with C_{max}, the AUC is a more reliable and stable measure. C_{max} measures drug exposure at an individual time point, whereas AUC reflects cumulative exposure over the entire dosing period. Unlike C_{max}, AUC is less sensitive to subtle differences in PK concentration collection times. Of note, USCAST used the AUC/MIC ratio for the basis of their evaluation of in vitro susceptibility test interpretive criteria for aminoglycosides, given the transient nature of C_{max} and the ability to estimate AUC with greater precision than the C_{max}.[14,35]

Integration of the AUC/MIC Ratio into Clinical Practice

Proposed AUC/MIC Ratio Targets

Unfortunately, the definitive AUC/MIC targets for therapy with many aminoglycosides are less clear, unlike those that exist for fluoroquinolones.[36] Evaluation of the literature indicates that AUC/MIC ratios typically associated with efficacy of certain aminoglycosides are approximately 30–100 for most studies. Mouton et al. demonstrated that an *f*AUC/MIC ratio of 50 provided maximal benefit when treating cystic fibrosis pulmonary infections with tobramycin; however, an important caveat was that all patients were also receiving ticarcillin in this study.[28] Craig et al. demonstrated that AUC_{0-24}/MIC ratios of

50 and 100 were associated with stasis and 1–2-log_{10} killing, respectively, when evaluating in vitro *K. pneumoniae* neutropenic mice.[13] This is largely consistent with pooled data analyses in the 2016 USCAST report and subsequent presentations that indicated that the AUC/MIC ratio targets required for stasis and 1-log_{10} CFU reduction from baseline were ~30 and ~80, respectively.[14,35,37,38] Smith et al., as stated previously, demonstrated higher clinical cure in patients with $AUC_{0–24}$/MIC ratios of > 110, irrespective of the infecting gram-negative pathogen.[27] Therefore, based on current literature, an AUC/MIC ratio of 30–50 for aminoglycoside therapy may provide optimal outcomes when targeting non–critically ill immunocompetent patients with low–bacterial burden gram-negative infections such as urinary tract infections, or in patients receiving additional gram-negative therapy with good source control. However, an AUC/MIC ratio target of 80–100 may be more prudent when treating patients with aminoglycoside monotherapy or in critically ill patients with high–bacterial burden infections, such as hospital-acquired pneumonia.[38] Further studies of AUC/MIC based dosing will help refine of the AUC/MIC ratio targets need for optimal response.

AUC Alone versus AUC/MIC Ratio–Guided Therapeutic Drug Management for Efficacy

Although the best available evidence suggests that the PK/PD driver for efficacy is the AUC/MIC ratio, it may be preferable to use the AUC alone versus the AUC/MIC ratio to optimize aminoglycoside dosing. Although the MIC informs the extent of exposure required for efficacy, it is important to recognize the inherent imprecision of MIC measurement, with a range of accuracy of $\pm 1_{log2}$ dilution and the high degree of variability between MIC testing methods. Furthermore, the MIC value is typically not available within the first 72 hours of index culture collection, if at all, across most institutions. Notably, the South Australian Expert Advisory Group on Antimicrobial Resistance (SAAGAR) has recently issued guidance recommending that high-dose, extended-interval aminoglycoside dosing should be guided by the AUC, which is more accurately estimated by two sample measurements.[39] Although the definitive target $AUC_{0–24}$ has not been fully elucidated, $AUC_{0–24}$ targets of 70–120 mg•hour/L have been proposed by some authors for gentamicin.[40,41] Alternatively, it would be reasonable, pending further data, to empirically target AUC/MIC ratios of 30–50 or 80–100, depending on the infection site and severity, until culture and susceptibility data are finalized. Once MIC values are available, dosing should be reevaluated.

The ability of commonly employed aminoglycoside dosing regimens to achieve these critical AUC/MIC ratio targets are best illustrated in the USCAST 2016 report and subsequent presentations.[14,35,37,38] Employing their proposed AUC/MIC ratio targets required for stasis and 1-$\log_{10}$ CFU reduction from baseline of ~30 and ~80, respectively, the simulations demonstrated that standard aminoglycoside regimens failed to achieve these PK/PD exposures for infections with MIC values at or near the current Clinical and Laboratory Standards Institute and FDA susceptibility breakpoints for gentamicin, tobramycin, and amikacin.[2-4,42] On the basis of the Monte Carlo simulations and MIC distributions among gram-negative bacteria observed in recent surveillance studies, USCAST has recommended lowering the susceptibility breakpoints for these aminoglycosides (Table 2[2-4,38,42-44]). Alternatively, doses of aminoglycoside that are higher than what is currently recommended would be needed to support these breakpoints, although safety data are limited to endorse such an approach at this time.

Therapeutic Drug Management for Toxicity

In addition to maximizing efficacy, one of the goals of therapeutic drug management for aminoglycosides is to minimize toxicity in patients.[45,46] Although there are data suggestive of AUC/MIC targets for efficacy, AUC targets for toxicity, in particular for acute kidney injury, are unclear. Previous studies have found that the daily aminoglycoside (amikacin, gentamicin, or tobramycin) AUC is a predictor of nephrotoxicity in patients with serious bacterial infections.[47,48] However, the daily and cumulative AUC threshold associated with acute kidney injury was primarily described in patients receiving traditional, multiple-daily dosing, and the AUC threshold for patients receiving once-daily dosing has not been well described. Until such data are available, clinicians should rely on more traditional approaches for monitoring drug levels to minimize toxicity. In the SAAGAR guidance document on aminoglycoside dosing and monitoring, it is recommended that clinicians aim for a gentamicin trough concentration of 0.5–1 μg/ml to minimize toxicity.[39] A similar trough is assumed for tobramycin, although most institutions maintain a laboratory trough set point of below 2 μg/ml to minimize toxicity. A specific trough target to minimize toxicity of amikacin is unclear based on a systematic review of the literature,[49] although most institutions recommend a trough below 5 μg/ml. For plazomicin, it is recommended that plasma trough concentrations should be maintained below 3 μg/ml when treating patients with complicated urinary tract infections and a creatinine clearance of 15–90 ml/minute.[5]

New Approaches for AUC-Guided Therapeutic Drug Management

Equation-based and Bayesian approaches can be used to estimate the AUC in clinical practice with limited PK sampling.[50,51] Equation-based approaches rely on simple first-order PK models that allow the daily AUC value to be calculated with reasonable accuracy from two concentration levels measured at expected peak (1–2 hours postinfusion) and a mid-dosing interval sample (8–12 hours after the start of the infusion) for high-dose, extended-interval dosing.[51,52] Subsequently, the equations can be programmed to compute the AUC automatically.[51] The equation-based approach provides a "real-world snapshot" of the patient's drug concentration profile (i.e., AUC) based on the patient's own serum concentration data.[51]

The Bayesian approach is based on Bayes' theorem and incorporates information about how a drug has behaved in prior patients as well as current PK information from the individual patient.[50,51] In short, the Bayesian approach takes into account the estimated probability distribution of an individual patient's PK parameter values (e.g., volume of distribution or clearance) before administering the drug based on the way the drug has behaved in prior patients (Bayesian prior). As dosing and concentration data become available, the probability distribution of a given patient's PK parameter values (Bayesian conditional posterior) will be revised. With the Bayesian conditional posterior, the AUC can be estimated with low bias and subsequent AUC-optimized dosing recommendations can be provided in real time.[51]

Software is readily available to implement the Bayesian approach at the patient's bedside,[51,53,54] and guidance for adopting this approach for the dosing of gentamicin and tobramycin has been published.[40,55,56] The Bayesian software requires only one or two serum concentrations to accurately calculate AUC, can support innovative dosing regimens, does not require waiting until steady state is reached to obtain the concentration sample, and can model covariates such as creatinine clearance that affect drug PK.[50,51] Recent studies have provided support for the AUC-guided, Bayesian approach to dosing for vancomycin.[57,58] Compared with trough-based concentration targets, the AUC-guided approach was shown to lead to decreased nephrotoxicity, reduced per-patient blood sampling, and shorter length of therapy, while maintaining efficacy.[58,59]

Future Directions

Knowledge of PK/PD parameters underlying the efficacy and safety of aminoglycosides has greatly expanded in recent years, with an emphasis on the importance of the AUC/MIC ratio as an appropriate index for aminoglycoside dosing. Additional research is needed to better define optimal AUC/MIC ratio targets for efficacy, especially when drugs are used in combination, as well as PK/PD targets associated with suppression of resistance. It is also important to determine if AUC can predict nephrotoxicity of these agents, or whether trough concentrations should be used instead. Frequency of monitoring trough concentrations (vs calculating the AUC) in patients with less severe infections, and thus having a lower risk of PK variability, requires further investigation. Finally, questions remain concerning the best methods to calculate AUC (equation-based or Bayesian) or via other software-based methods.

Conclusion

Aminoglycosides are useful agents for the treatment of infections caused by MDR gram-negative pathogens. Our recent improved understanding of the PK/PD parameters of these agents has helped identify appropriate targets for dosing aminoglycosides to ensure exposure to a therapeutic dose while minimizing risk of toxicity. The AUC/MIC ratio has emerged as a particularly important guide for optimal dosing of these agents. New approaches that can be implemented through readily available software tools allow the practitioner to estimate drug exposure for individual patients, with sufficient accuracy to meet the appropriate AUC/MIC ratio target. With greater confidence in effective dosing, clinicians can add aminoglycosides back into their toolkit to combat MDR pathogens.

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Table 1. U.S. Guideline Recommendations for the Use of Legacy Aminoglycosides to Treat Severe Infections

Guideline	Recommendation for Aminoglycoside Treatment	Strength of Recommendation, Quality of Evidence	Agent[a] and Dose
Infectious Diseases Society of America: Acute Pyelonephritis[6]	If the prevalence of fluoroquinolone resistance exceeds 10%, a consolidated 24-hr dose of an aminoglycoside is recommended	Moderate recommendation, low-quality evidence	Gentamicin 5–7 mg/kg IV daily
Infectious Diseases Society of America: HAP/VAP[7]	A potential option as combination therapy for patients with HAP who have a high risk of mortality	Not stated	Amikacin 15–20 mg/kg IV daily Gentamicin 5–7 mg/kg IV daily Tobramycin 5–7 mg/kg IV daily
	Should be avoided in patients with VAP if alternative agents with adequate gram-negative activity are available	Weak recommendation, low-quality evidence	
Infectious Diseases Society of America: Intravenous Catheter-	As combination therapy for bloodstream infection due to *Enterococcus* spp. or *Pseudomonas*	Strong recommendation, medium-quality evidence	Gentamicin 1 mg/kg IV every 8 hrs (*Enterococcus* spp.)

Related Infections[8]	*aeruginosa*		Amikacin 15 mg/kg IV daily (*P. aeruginosa*) Tobramycin 5–7 mg/kg IV daily (*P. aeruginosa*)
Surviving Sepsis Campaign Guidelines Committee: Sepsis and Septic Shock[9]	As combination therapy for sepsis and septic shock, except in patients with severe renal impairment	Weak recommendation, low-quality evidence	Gentamicin 5–7 mg/kg IV daily
American Heart Association: Infective Endocarditis[10]	As combination therapy for infective endocarditis caused by *Streptococcus*, *Enterococcus*, and *Staphylococcus* spp.	Moderate recommendation, medium-quality evidence (*Streptococcus* spp. and *Enterococcus* spp.) Strong recommendation, medium-quality evidence (*Staphylococcus* spp.)	Gentamicin 3 mg/kg IV or IM in 1 dose or in 3 equally divided doses daily (*Streptococcus* spp.) Gentamicin 3 mg/kg ideal body weight daily in 2–3 equally divided doses (*Enterococcus* spp.[b] and *Staphylococcus* spp.)

HAP = hospital-acquired pneumonia; VAP = ventilator-associated pneumonia.

[a]Amikacin, gentamicin, and tobramycin only; plazomicin was approved in 2018 and is therefore not yet included in these guidelines.

[b]Gentamicin dose should be adjusted to achieve a peak serum concentration of 3–4 μg/ml and trough serum concentration of < 1 μg/ml when three divided doses are used.

Table 2. Current and Proposed Aminoglycoside Susceptibility Breakpoints for *Enterobacteriaceae*, *Pseudomonas* spp., and *Acinetobacter* spp.[2-4,38,42-44]

	Recommended Breakpoint (μg/ml)								
	Enterobacteriaceae			*Pseudomonas spp.*			*Acinetobacter*[a] *spp.*		
Agent (Dose)	Susceptible	Intermediate	Resistant	Susceptible	Intermediate	Resistant	Susceptible	Intermediate	Resistant
Amikacin (20–30 mg/kg)									
EUCAST[43]	≤ 8	16	> 16	≤ 8	16	> 16	≤ 8	16	> 16
CLSI[42]	≤ 16	32	≥ 64	≤ 16	32	≥ 64	≤ 16	32	≥ 64
FDA[2]	≤ 16	32	≥ 64	≤ 16	32	≥ 64	≤ 16	32	≥ 64
USCAST[38]	≤ 4	–	≥ 8	≤ 2	–	≥ 8	–	–	–
Gentamicin (5–7.5 mg/kg)									
EUCAST[43]	≤ 2	4	> 4	≤ 4	–	> 4	≤ 4	–	> 4
CLSI[42]	≤ 4	8	≥ 16	≤ 4	8	≥ 16	≤ 4	8	≥ 16
FDA[3c]	≤ 4	8	≥ 16	≤ 4	8	≥ 16	–	–	–

USCAST[38] Non-pneumonia	≤ 2	–	≥ 4	–	–	–	–	–	–
USCAST[38] Pneumonia	≤ 1	–	≥ 4	–	–	–	–	–	–
Tobramycin (5–7.5 mg/kg)									
EUCAST[43]	≤ 2	4	> 4	≤ 4	–	> 4	≤ 4	–	> 4
CLSI[42]	≤ 4	8	≥ 16	≤ 4	8	≥ 16	≤ 4	8	≥ 16
FDA[4]	≤ 4	8	≥ 16	≤ 4	8	≥ 16	–	–	–
USCAST[38] Non-pneumonia	≤ 2	–	≥ 4	≤ 1	–	≥ 2	–	–	–
USCAST[38] Pneumonia	≤ 1	–	≥ 4	–	–	–	–	–	–
Plazomicin (15 mg/kg)									
FDA[44]	≤ 2	4	> 8	–	–	–	–	–	–

CLSI = Clinical and Laboratory Standards Institute; EUCAST = European Committee on Antimicrobial Susceptibility Testing; FDA = U.S. Food and Drug Administration; USCAST = National Antimicrobial Susceptibility Testing Committee for the United States.

[a]Amikacin is the only aminoglycoside to have an indication for *Acinetobacter* spp. by U.S. regulators.

Figure 1. The relationship between different pharmacokinetic/pharmacodynamic indices and change in the number of bacteria for amikacin in the thighs of neutropenic mice. The R^2 value reflects the coefficient of determination.

CFU = colony-forming units; MIC = minimum inhibitory concentration; AUC = area under the plasma concentration–time curve.

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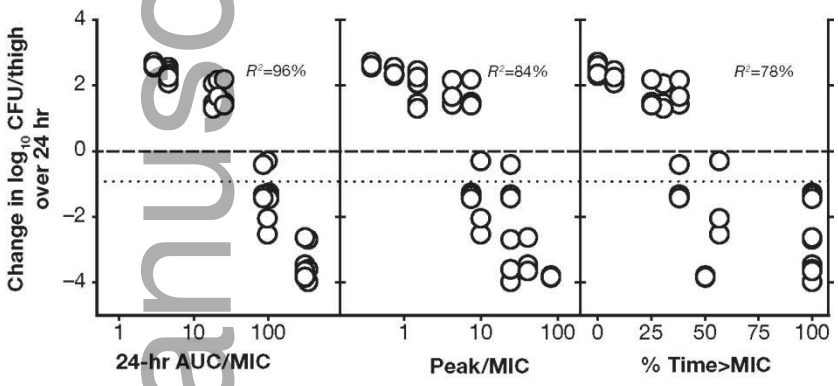

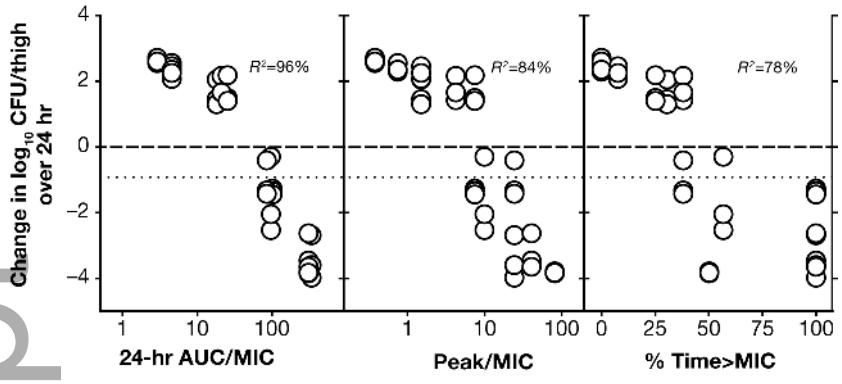

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