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Evaluating the incidence of acute kidney injury and gentamicin synergy dosing for endocarditis

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Objectives: Current infective endocarditis guidelines recommend two different gentamicin synergy dosing strategies for selected Gram-positive organisms. The purpose of this analysis was to evaluate the incidence of acute kidney injury (AKI) with gentamicin synergy dosing, comparing divided-daily and once-daily dosing strategies for infective endocarditis (IE).

Methods: Groups were split into patients who received gentamicin divided-daily dosing and once-daily (3 mg/kg) dosing for Gram-positive IE. The primary outcome was the incidence of AKI defined by RIFLE (risk, injury, failure, loss, end-stage renal disease) criteria after starting gentamicin. A multivariable logistic regression analysis was performed to identify possible independent predictors of developing AKI. Notable secondary outcomes included hospital length of stay, need for gentamicin dose adjustments based on therapeutic drug monitoring, and assessment of each case of AKI using the Naranjo algorithm.

Results: The incidence of AKI was significantly higher in the divided-daily group compared with the once-daily group (52.5% versus 13%, $P<0.01$). The divided-dosing group had significantly longer median [IQR] hospital length of stay (19 days [12:29] versus 13.5 days [9:22], $P<0.01$) and a greater number of patients who required dose adjustments (76.2% versus 21.7%, $P<0.01$). The multivariable regression analysis showed that the divided-dosing strategy, duration and institution were independently associated with incidence of AKI.

Conclusions: This analysis suggests a lower incidence of AKI in the treatment of endocarditis with gentamicin synergy dosed once-daily compared with a divided-daily dosing. Further studies are warranted to assess if there is a difference in efficacy between gentamicin synergy dosing strategies and in gentamicin compared with no gentamicin regimens for IE.

Introduction

Infective endocarditis (IE) is a life-threatening disease with high morbidity and mortality.[1] The modified Duke criteria provide the framework for diagnosing IE, and treatment typically involves medical management with antimicrobials, surgery or a combination of the two.[2] The most common causative pathogens of IE are *Staphylococcus aureus*, viridans group streptococci and *Enterococcus faecalis*.[2,3] Antimicrobial recommendations consider the pathogen-specific MIC, inoculum effect, drug penetration and bactericidal effects.[3]

Treatment of IE may involve the use of aminoglycosides in synergy with other antimicrobials depending on the organism and the presence of a native or prosthetic valve.[4] Certain antimicrobials (i.e. penicillins, cephalosporins, vancomycin) damage the cell wall and allow the uptake of gentamicin intracellularly. This process enhances the bactericidal properties of gentamicin to optimize organism killing.[3] The 2015 American Heart Association/Infectious Diseases Society of America guidelines recommend two different gentamicin synergy dosing strategies. In non-streptococcal infections, the guidelines recommend gentamicin synergy dosing at 3 mg/kg in two or three equally divided doses every 24 h; however, for streptococcal infections, the guidelines offer 3 mg/kg once every 24 h as an alternative regimen based on data from a previous randomized controlled trial.[3,5]

Aminoglycoside-induced nephrotoxicity is well described in the literature and manifests as proximal tubular epithelial cell damage.[6–8] These effects appear to be saturable and related to exposure at the epithelial cell level, with the incidence of nephrotoxicity not necessarily increasing as the dose increases.[7] Studies have

demonstrated a lower incidence of nephrotoxicity using high-dose extended-interval aminoglycoside regimens for Gram-negative infections.[6] It is unclear if there is a difference in nephrotoxicity incidence between dosing strategies for Gram-positive synergistic treatment for IE.

The purpose of this analysis was to evaluate the incidence of acute kidney injury (AKI) with gentamicin synergy dosing, comparing once-daily and divided-daily dosing strategies for IE.

Materials and methods

We conducted a multicentre, retrospective, observational analysis at Brigham and Women's Hospital and Massachusetts General Hospital in Boston, Massachusetts. The Mass General Brigham institutional review board (IRB) approved the study prior to its initiation (IRB protocol # 2022P002241). Institutional electronic health records were used to identify all adult patients who received gentamicin synergy dosing at 3 mg/kg once daily (once-daily dosing group) or 3 mg/kg in two or three equally divided doses daily (divided-daily dosing group) for IE between 1 July 2015 and 30 August 2022. Both institutional protocols recommend divided-daily dosing of gentamicin for endocarditis caused by *Enterococcus* spp. or *Staphylococcus* spp. (Table 1), while recommending once-daily dosing as an alternative strategy for endocarditis caused by *Streptococcus* spp. IE was defined using the Duke criteria.[9] Patients were excluded from the analysis if they required renal replacement therapy prior to gentamicin initiation, received a dosing regimen outside of the prespecified regimens included in the analysis, if there was no consistent dosing regimen for at least 48 h during the gentamicin course, or if patient data were unavailable from outside hospital records within 24 h of gentamicin initiation.

Data collected at baseline included patient demographics, serum creatinine and glomerular filtration rate (GFR). Creatinine clearance was separately calculated using either adjusted or ideal body weight via the Cockcroft–Gault equation, with no serum creatinine age correction. If the total body weight was greater than or equal to 120% of ideal body weight, adjusted body weight was used to calculate creatinine clearance. Upon gentamicin initiation, the SOFA score, serum creatinine, GFR, initial dosing regimen and infectious organism were collected. Therapeutic drug monitoring (TDM), peak serum creatinine, lowest GFR and concomitant nephrotoxic agents within 24 h of peak serum creatinine were collected during gentamicin therapy.

The major outcome of this analysis was incidence of AKI defined by the RIFLE criteria (risk, injury, failure, loss, end-stage renal disease) after initiating gentamicin.[10] Due to inconsistent documentation of urine output and the retrospective nature of the study, a modified version of the RIFLE criteria was used to define AKI: an acute increase in serum creatinine of 50% within 7 days, or GFR reduction by 25% from baseline. Minor outcomes included RIFLE criteria severity classification, number of patients with gentamicin dose adjustments, requirement for renal replacement therapy and hospital length of stay (LOS). The likelihood of gentamicin-induced nephropathy in cases of AKI was assessed using the Naranjo algorithm.

Continuous data were analysed using a *t*-test (parametric data, expressed as mean [SD]) or Mann–Whitney *U* test (non-parametric data, expressed as median [IQR]) when appropriate. Chi-square test or Fisher's exact test were used when appropriate for categorical data. A multivariable logistic regression analysis was conducted to identify possible independent predictors of developing AKI. Variables included in the analysis were chosen a priori based on theoretical impact on impaired renal function: dosing strategy, age, duration of gentamicin, BMI, institution, and number of concomitant nephrotoxic agents.

Results

A total of 245 patients were evaluated for inclusion, of whom 147 patients met the inclusion criteria. Of those included, 101 patients were in the divided-daily dosing group and 46 patients were in the once-daily dosing group. The most common reasons for exclusion were no consistent dosing regimen for at least 48 h during the gentamicin course and incomplete data within 24 h of starting gentamicin given outside hospital transfers (Figure 1). Patient demographics and SOFA scores were similar between groups (Table 2). The divided-daily dosing group had more concomitant vancomycin administrations. Creatinine clearance was overall lower in the divided-daily dosing group; however, serum creatinine was similar between groups. Treatment of *Staphylococcus aureus* or *Enterococcus* spp. was more often seen in the divided-daily dosing group, whereas treatment of viridans group streptococci was more often seen in the once-daily dosing group.

Table 1. Hospital-specific gentamicin synergy divided daily dosing guidelines for infective endocarditis based on adjusted body weight

Institution 1	Institution 2
• >70 mL/min CrCl: 1 mg/kg q8h	• ≥70 mL/min CrCl: 1 mg/kg q8h
• 45–70 mL/min CrCl: 1 mg/kg q12h	• 50–69 mL/min CrCl: 1 mg/kg q12h
• 25–44 mL/min CrCl: 1 mg/kg q24h	• 30–49 mL/min CrCl: 1 mg/kg q18–q24h
• <25 mL/min CrCl: 1 mg/kg load, then dose by level	• 20–29 mL/min CrCl: 1 mg/kg q24–36h
	• <20 mL/min CrCl or acute renal insufficiency: 1 mg/kg load, then dose by level

CrCl, creatinine clearance.

The incidence of AKI was significantly higher in the divided-daily dosing group compared with the once-daily dosing group (52.5% versus 13%, $P < 0.01$) (Table 3). Time to AKI in the divided-daily dosing group was 7 days [4:11] compared with 4 days [3:7] in the once-daily dosing group. There was no difference in RIFLE AKI classification, requirement for renal replacement therapy or inpatient mortality. The divided-daily dosing group had a significantly longer hospital LOS (19 days [12:29] versus 13.5 days [9:22], $P < 0.01$) and greater number of patients who required dose adjustments (76.2% versus 21.7%, $P < 0.01$) than the once-daily dosing group. The number of gentamicin concentrations documented were totalled for each group. There were 476 concentrations documented in the divided-daily dosing group associated with 149 dose adjustments (31.3%). The once-daily dosing group had 113 documented concentrations associated with 13 dose adjustments (11.5%). Of the 92 patients originally started on an 8 h or 12 h dosing frequency, 36 (39.1%) were extended to a 24 h or longer dosing frequency due to supratherapeutic concentrations, defined by the institution as trough concentrations >0.5 mg/dL (institution 1) or >1 mg/dL (institution 2). Of the 59 patients who developed AKI, 32 patients discontinued gentamicin within 24 h of AKI occurrence. For patients who developed an AKI, the average Naranjo algorithm score was 3 in both groups, indicating possible gentamicin-induced AKI.

No patients received once-daily dosing for *Staphylococcus aureus* endocarditis. A subgroup analysis of 105 patients was performed, excluding those with *S. aureus*, to account for the potential that patients with *S. aureus* endocarditis may have been more likely to develop AKI. The incidence of AKI remained statistically significantly higher in the divided-daily dosing group

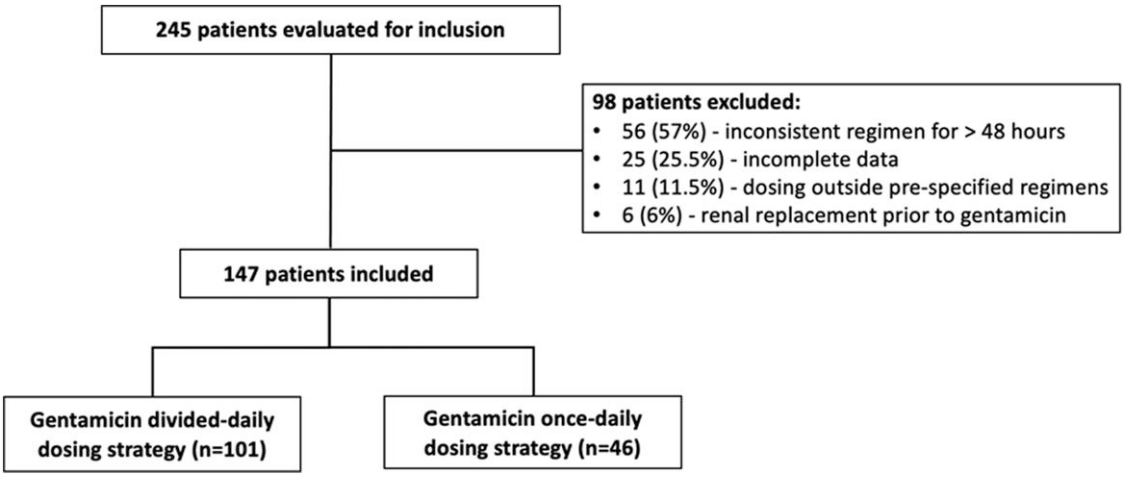

Figure 1. Patient exclusion.

compared with the once-daily dosing group in this subgroup (45.8% versus 13%; $P < 0.01$).

A multivariable logistic regression analysis of the overall study population was performed to identify independent predictors associated with the incidence of AKI. When controlling for confounders, divided-daily dosing, duration of gentamicin and the institution of administration were significantly associated with development of AKI (Table 4). The odds of developing AKI in the once-daily dosing group were 85% lower than the divided-daily dosing group, and every additional day of gentamicin was associated with a 12% increase in risk of AKI. Age, BMI and the number of concomitant nephrotoxic agents did not show an impact in development of AKI in our population.

Discussion

In this retrospective analysis, patients receiving gentamicin in a divided-daily dosing regimen had significantly higher rates of nephrotoxicity, required more dose adjustments and experienced significantly longer hospital LOS compared with patients receiving a once-daily dosing regimen. To our knowledge, this is the first study that has evaluated the incidence of AKI between gentamicin synergy dosing regimens for the treatment of IE.

A meta-analysis published by Barza *et al.*[6] evaluated the efficacy and safety of different aminoglycoside dosing regimens for Gram-negative infections, and found patients treated with once-daily dosing regimens were associated with less nephrotoxicity than divided-daily dosing regimens. For Gram-positive infections, a prospective study published by Buchholtz *et al.*[8] evaluated the nephrotoxic effects of gentamicin versus no gentamicin in patients with IE and found the mean decrease in creatinine clearance was 8.6% in the gentamicin group versus a mean increase of 2.3% in the no gentamicin group ($P < 0.01$). Of note, most of the patients included in this analysis received divided-daily doses of gentamicin and did not include information evaluating nephrotoxicity of different dosing regimens. Our study analysed nephrotoxicity between gentamicin synergy dosing strategies for Gram-positive organisms and found less nephrotoxicity occurred with a once-daily dosing regimen.

A multivariable regression analysis was conducted to analyse independent risk factors associated with the incidence of AKI. When controlling for confounders, our findings were consistent with the major outcome, demonstrating that a divided-daily dosing regimen was an independent risk factor for developing AKI. An additional independent risk factor of AKI identified in the analysis was longer duration of gentamicin treatment. This is comparable to previous studies assessing risk factors of AKI in patients receiving gentamicin for IE.[8,11] Infective organisms were collected, but the study's primary objective was built from a safety perspective and not focused on clinical cure; thus, we hypothesized that differences in AKI rates among organisms did not contribute to the major outcome of this study. Patients with *S. aureus* IE often present with a sudden onset of systemic complications, which can lead to AKI, mortality and a longer hospital LOS.[2] To account for this, a subgroup analysis was conducted where patients with *S. aureus* IE were excluded. This parameter excluded 42% of patients in the divided-daily dosing group. Even with this population excluded in the subgroup analysis, a statistically significantly higher rate of AKI was noted in the divided-daily dosing group.

There are several limitations to this study. First, it was a retrospective study; thus, we were reliant on the accuracy of the electronic medical record. Data were only collected on patients while they were admitted to the hospital. If patients were continued on gentamicin following hospital discharge, these data were not included in the study. Additionally, we used the RIFLE criteria to diagnose AKI. This method could have missed diagnoses of AKI that other methods of assessing AKI may have detected. This study also did not account for a control group not using gentamicin synergy for IE, limiting our ability to extrapolate the impact of gentamicin as a whole on the incidence of AKI in our patients with endocarditis. Another limitation is the potential difference between patient groups with regard to the infecting organism. Endocarditis due to viridans group streptococci accounted for 76% of cases in the once-daily dosing group, with the divided-daily dosing group commonly involving *Enterococcus* spp. or *S. aureus*. Although the presentation and prognosis for these patients can be quite different, the objective of this study was

Table 2. Baseline characteristics

	Divided-daily dosing ($n=101$)	Once-daily dosing ($n=46$)
Gender, female[a]	31 (30.7)	11 (23.9)
Age,[b] y	56 [34:70]	52.5 [36:69]
Race[a]		
White	82 (81.2)	42 (91.3)
Black	5 (5)	1 (2.2)
Asian	1 (1)	0
Other	13 (12.8)	3 (6.5)
Weight,[b] kg	80 [70:96]	80 [71:89]
Ideal body weight,[b] kg	69 [62:75]	71 [59:75]
Height,[b] cm	175 [166:180]	173 [163:180]
Institution[a]		
Institution 1	30 (29.7)	16 (34.8)
Institution 2	71 (70.3)	30 (65.2)
SOFA score[b]	1 [0:3]	0 [0:1]
Creatinine clearance,[a] mL/min	88.3 [63.5:107.1]	107.6 [76.4:128.8]
Serum creatinine (prior to gentamicin)[b]	0.9 [0.7:1.1]	0.8 [0.7:0.9]
GFR (prior to gentamicin)[a]		
<15	1 (1)	0
15–29	1 (1)	0
30–44	6 (5.9)	0
45–59	8 (7.9)	4 (8.7)
>59	85 (84.2)	42 (92.3)
Infective organism[a]		
Staphylococcus aureus	42 (41.6)	0
Viridans group streptococci	3 (3)	35 (76.1)
Enterococcus spp.	15 (14.9)	1 (2.2)
Coagulase-negative staphylococcus	13 (12.9)	1 (2.2)
Streptococcus bovis	8 (7.9)	2 (4.3)
Granulicatella spp.	1 (1)	2 (4.3)
Other[c]	19 (18.8)	6 (13)
Concomitant nephrotoxins[a]		
Loop diuretic	50 (49.5)	19 (41.3)
Cephalosporin	48 (47.5)	33 (71.7)
Vancomycin	48 (47.5)	8 (17.4)
Contrast	20 (19.8)	10 (21.7)
NSAID	10 (9.9)	7 (15.2)
ACEi/ARB	9 (8.9)	4 (8.7)
Nafcillin	10 (9.9)	0

ACEi/ARB, angiotensin-converting enzyme inhibitor/angiotensin II receptor blockers; GFR, glomerular filtration rate; NSAID, non-steroidal anti-inflammatory drug; SOFA, Total Sequential Organ Failure Assessment.

[a]Presented as *n* (%).

[b]Presented as median [IQR].

[c]Other: group B streptococcus ($n=5$), *Abiotrophia* spp. ($n=3$), *Corynebacterium jeikeium* ($n=2$), *Lactobacillus* spp. ($n=3$), *Propionibacterium acnes* ($n=3$), *Neisseria mucosa* ($n=1$), *Gemella haemolysans* ($n=1$), *Lactococcus garvieae* ($n=1$), Gram-positive clusters that failed to speciate ($n=1$), culture negative ($n=3$).

centred around safety, as opposed to clinical cure, therefore likely does not impact the conclusions of this analysis.

Although our study highlights the decreased incidence of AKI with the once-daily dosing group, discussion on the role of aminoglycosides in IE is warranted. A systematic review conducted by Lebeaux *et al.*[12] suggests that gentamicin therapy could be avoided in ~90% of IE cases. In cases where aminoglycosides are utilized, studies proving similar efficacy between gentamicin dosing strategies for non-streptococcal infections are limited primarily to *in vitro* data and animal studies.[13,14] Although our study suggests that once-daily dosing may have less incidence of AKI compared with divided-daily dosing, there is a paucity of literature

Table 3. Primary and secondary outcomes

	Divided-daily dosing ($n=101$)	Once-daily dosing ($n=46$)	*P* value
AKI[a]	53 (52.5)	6 (13)	<0.01
AKI classification[a]			
Risk	38 (71.7)	5 (83.3)	0.37
Injury	14 (26.4)	1 (16.7)	0.27
Failure	1 (1.9)	0	—
Renal replacement therapy[a]	1 (1)	0	—
Inpatient mortality[a]	9 (8.9)	3 (6.5)	0.24
Hospital LOS[b]	19 [12:29]	13.5 [9:22]	<0.01
Number of patients with dose adjustments[a]	77 (76.2)	10 (21.7)	<0.01
Naranjo score[b]	3 [3:4]	3 [2:3]	0.42

AKI, acute kidney injury; LOS, length of stay.
[a]Presented as n (%).
[b]Presented as median [IQR].

Table 4. Multivariable analysis to predict independent risk factors of AKI

	OR	95% CI	*P* value
Once-daily dosing regimen	0.15	0.05–0.40	<0.01
Age	1.01	0.99–1.04	0.32
Duration of gentamicin	1.12	1.05–1.20	<0.01
BMI	1.03	0.96–1.09	0.41
Institution 1	0.26	0.01–0.67	<0.01
Number of nephrotoxic agents	1.37	0.95–1.97	0.09

evaluating the efficacy of these different dosing regimens. Further studies comparing dosing strategies, or regimens that do or do not contain gentamicin for synergy, would be beneficial.

Conclusion

Our analysis suggests a lower incidence of AKI, shorter hospital LOS and fewer dose adjustments in the treatment of endocarditis with gentamicin synergy dosed once-daily compared with a divided-daily dosing strategy.

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Transparency declarations

The authors declare no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

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