Low-dose Gentamicin for Uncomplicated *Enterococcus faecalis* Bacteremia May be Nephrotoxic in Children

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(See the Editorial Commentary by Driest and Goldman on pages 1125–6.)

**Background.** Uncertainty exists regarding the role of synergistic gentamicin for uncomplicated *Enterococcus faecalis* bacteremia in children.

**Methods.** We conducted a retrospective, observational study comparing clinical outcomes of children with *E. faecalis* bacteremia without endocarditis receiving ampicillin monotherapy with those receiving ampicillin along with low-dose gentamicin therapy. To account for nonrandom assignment of combination therapy, propensity score weighting was combined with multivariable regression to estimate the effect of combination therapy on duration of bacteremia, bacteremic relapse, and acute kidney injury (AKI).

**Results.** One hundred sixty-three (52%) patients received ampicillin with low-dose gentamicin, and 150 (48%) patients received ampicillin monotherapy. Incorporating propensity-score weighting with additional adjustment for source control measures, patients receiving combination therapy experienced bacterial clearance 10 hours faster than children receiving ampicillin monotherapy (adjusted mean difference 0.42; confidence interval (CI), 0.02 to .82; *P* = .04). Bacteremic relapse was similar between the two groups (17% vs 18%); adjusted hazards ratio (aHR) 1.12; 95% CI, .65 to 1.92. Children receiving low-dose gentamicin had approximately twice the risk of developing AKI compared to children not receiving this agent, adjusting for the receipt of additional nephrotoxins (aHR 1.94; 95% CI, 1.48–2.97).

**Conclusions.** Our study suggests that for children with uncomplicated *E. faecalis* bacteremia, the addition of low-dose gentamicin may decrease the time to bacterial clearance by 10 hours but without any impact on recurrent bacteremia. However, with this potential benefit comes the increased likelihood of AKI. Low-dose gentamicin for the treatment of uncomplicated enterococcal bacteremia may pose harm to children with limited benefit.

**Keywords.** *Enterococcus faecalis*; gentamicin; synergy; aminoglycosides; pediatrics.

With advancements in medical care, greater numbers of children are requiring indwelling central venous catheters [1]. Although this provides improved nutrition, chemotherapy, and fluid resuscitation, it also places children at increased risk of catheter-related infections with organisms such as *Enterococcus faecalis*. The optimal management of enterococcal bacteremia remains unclear. The 2009 Infectious Diseases Society of America guidelines state, “The role of combination therapy (ie, a cell wall active antimicrobial and an aminoglycoside) for treating enterococcal CRBSI [catheter-related bloodstream infections] without endocarditis is unresolved (CII)” [2].

Early in vitro studies demonstrated a benefit with synergistic gentamicin for the inhibition of bacterial cell wall synthesis [3, 4]. This practice has been shown to improve outcomes and has become the standard of care for the
treatment of infective endocarditis [5–7]. However, few studies compare the role of ampicillin alone vs ampicillin in combination with low-dose gentamicin for the treatment of enterococcal bacteremia in the absence of cardiac valve involvement. Existing studies are limited by small sample sizes and failure to account for differences in baseline characteristics between the comparison groups, making it difficult to draw conclusions [8–11]. Additionally, there are no studies specific to the pediatric population evaluating the different treatment strategies.

Although it is uncertain whether the addition of an aminoglycoside to ampicillin provides added benefit for uncomplicated bacteremia (in the absence of endocarditis), synergistic aminoglycosides may result in avoidable harm. In a study of adults with Staphylococcus aureus bacteremia and native valve endocarditis, low-dose gentamicin (1 milligram per kilogram per dose administered every 8 hours) was found to be nephrotoxic [12], Standard dosing of gentamicin (2.5 mg per kg per day administered every 8 hours) has been previously shown to be nephrotoxic in children [13], but the potential toxicity of lower-dose gentamicin has not been explored in this population. We conducted a retrospective cohort study of pediatric patients with enterococcal bacteremia without endocarditis or suppurative thrombophlebitis (“uncomplicated bacteremia”) and compared duration of bacteremia, bacteremic relapse, and subsequent risk of acute kidney injury (AKI) for children receiving ampicillin alone compared with those receiving ampicillin and gentamicin.

**METHODS**

**Setting and Participants**

All patients between the ages of 1 year and 18 years (inclusive) who had a positive blood culture for *E. faecalis* as identified by the Johns Hopkins Hospital clinical microbiology laboratory from 1 January 2004 until 31 March 2014 with any of the following clinical signs and symptoms suggestive of infection using age-based normal values were evaluated for inclusion in this study: temperature >38° or <36°C, leukopenia, leukocytosis, apnea, bradycardia, tachycardia, or hypotension [14]. Patients were excluded if they (1) had polymicrobial bacteremia; (2) received ampicillin for less than 5 days; (3) received full-dosed gentamicin or streptomycin; (4) had endocarditis or suppurative thrombophlebitis; (5) had *E. faecalis* isolates with in vitro resistance to the antibiotic therapy prescribed, according to the Clinical and Laboratory Standards Institutions criteria; or (6) required renal replacement therapy prior to the first day of detectable bacteremia. For children who experienced greater than 1 episode of bacteremia due to *E. faecalis* during the study period, only the first episode was included.

**Data Collection**

Laboratory databases were queried to identify all blood cultures from which *E. faecalis* was isolated during the study period. All patient data were extracted from medical records. The primary exposure was receipt of ampicillin with or without low-dose (1 mg per kg) gentamicin that was initiated within 24 hours of organism and antibiotic susceptibility identification.

Outcomes of interest included (a) duration of bacteremia; (b) bacteremic relapse; and (c) AKI. Duration of bacteremia was defined as the difference between the time (in hours) the first negative blood culture was obtained and the time the first positive blood culture was obtained. It is standard practice at The Johns Hopkins Hospital for children with *E. faecalis* bacteremia to have daily blood cultures evaluated until there is no further detectable bacterial growth. A bacteremic relapse was documented if a second episode of *E. faecalis* bacteremia occurred after 7 days of negative blood cultures following the initial episode until 60 days after antibiotics were discontinued.

Children were categorized as having AKI if they met any of the categories included in the pediatric modified RIFLE criteria [15]. RIFLE (Risk for renal dysfunction, Injury to the kidney, Failure of kidney function, Loss of kidney function, and End-stage renal disease) stratifies children based on changes in estimated creatinine clearance (CrCL) from baseline and/or changes in urine output (UOP). Children were categorized according to the maximum RIFLE class reached up to 72 hours after discontinuation of antibiotics. Baseline serum creatinine (Scr) was determined using the lowest Scr (using the enzymatic method) measured at any time within the week prior to the onset of bacteremia (if available) and if not, within 72 hours after the first positive blood culture was obtained. This time period was selected because of the possibility of a temporary rise in the Scr from hypoperfusion to the kidneys during a systemic inflammatory response. CrCL was estimated using the Bedside Schwartz equation (CrCL = (0.413 × height (centimeters)) ÷ Scr (mg/dL)). Risk was defined as a decrease in estimated CrCL by 25% of baseline and/or UOP of <0.5 milliliters per kilogram per hour for at least 8 hours; injury involved a decrease in estimated CrCL by at least 50% and/or a decrease in UOP of <0.5 mL per kg per hour for at least 16 hours; and failure referred to a decreased in estimated CrCL by 75% and/or UOP of <0.3 mL per kg per hour for at least 24 hours or anuria for at least 12 hours.

Additional data retrieved through chart review included the following: (1) demographics; (2) preexisting medical conditions; (3) immunosuppressed status, which included one or more of the following: ≥2 mg per kg of prednisone for at least 14 days, immunomodulator therapy, hematopoietic stem cell transplant within 1 year prior to onset of bacteremia, solid organ transplant, cancer chemotherapy within 6 months prior to onset of bacteremia, congenital immunodeficiency, and human immunodeficiency virus positive with CD4 <200 cells/mm³.
[16]; (4) highest Pitt bacteremia score, intensive care unit (ICU) admission, mechanical ventilation, and/or pressor requirement, all on the first day a positive blood culture was obtained; (5) source control (ie, removal of central venous catheters during the time of antibiotic treatment, drainage of intra-abdominal fluid collections); and (6) use of intravenous contrast or >48 hours of nephrotoxins (acyclovir, amphotericin, cidofovir, cisplatin, colistin, cyclosporine, fosfomycin, cyclophosphamide, methotrexate, nonsteroidal anti-inflammatory drugs or vancomycin) collected as dichotomous variables. This study was approved by the Johns Hopkins University School of Medicine Institutional Review Board, with a waiver of informed consent.

Statistical Analysis
Demographic and clinical characteristics were summarized as percentages for categorical variables and means and standard deviations for continuous variables. As it was anticipated that the distribution of these characteristics may differ between the children who received combination therapy and those who received ampicillin monotherapy, propensity scores were created to establish each patient’s probability of receiving synergistic gentamicin as definitive therapy.

We estimated propensity scores for the use of combination therapy for each of the 313 patients using multivariable logistic regression. Variables included in the model were as follows: age, preexisting medical conditions, immunocompromised status, ICU admission, vasopressor requirement, source of bacteremia, baseline CrCl in categories (>60, 30–60, 10–29, <10; all in mL/min/1.73 m^2), and mechanical ventilation.

The average treatment effect that we would have observed had the entire population been treated with combination antibiotic therapy was chosen as the estimand. Patients receiving combination therapy were weighted by the inverse of the probability of receiving combination therapy, and those receiving monotherapy were weighted by the inverse of the probability of receiving monotherapy. Covariate balance after weighting was evaluated using the absolute standardized mean difference, the t-test for continuous variables, and Pearson χ^2 test for categorical values. The performance of the weighted sample was assessed using standardized mean differences, with values of 0.20 or less indicating adequate balance.

Mean difference for the duration of bacteremia and hazard ratios (HRs) for bacteremic relapse and AKI comparing the combination therapy group and monotherapy group were estimated in unweighted univariable analysis using linear regression models and Cox proportional hazards models, respectively. Covariates with \( P < .20 \) in the univariable model were entered into an adjusted model integrating weighting and additional potential confounders determined a priori including source control for the outcomes of duration of bacteremia and bacteremic relapse and use of additional nephrotoxins when evaluating AKI. For all statistical tests, two-sided \( P \)-values of < .05 were considered to be statistically significant. Data were analyzed using Stata, version 11.1 (StataCorp, College Station, Texas) and the twang package for the R programming language version 2.14.1 (R Development Core Team, Vienna, Austria) [17].

RESULTS

Study Population
During the study period, 313 cases of \( E. \) faecalis bacteremia met eligibility criteria. There were 163 (52%) patients receiving ampicillin with low-dose gentamicin dosed at 1 mg per kg every 8 hours, or an equivalent dosage adjustment for renal insufficiency (“combination therapy”) and 150 (48%) patients receiving ampicillin monotherapy. The median dose of ampicillin was 75 mg per kg per dose every 6 hours. For children receiving low-dose gentamicin, there was a median of 3.1 gentamicin levels obtained per patient for therapeutic drug monitoring purposes. For the 54% of children in the combination group who had gentamicin peaks and troughs obtained, the median peak of gentamicin was 3.7 mcg/mL and the median trough was 0.4 mcg/mL.

A comparison of patient characteristics within each treatment group is displayed in Table 1. Patients in the combination therapy group were more likely to be in the ICU, require vasopressors and mechanical ventilation, and have a compromised immune system. Patients in the ampicillin monotherapy arm were more likely to have a lower baseline CrCl and/or have chronic kidney disease.

The most common source of bacteremia in each group was a central venous catheter. Among patients with catheter-related bloodstream infections, the central line was removed in 43 (43%) patients within the combination therapy group and 66 (44%) patients within the ampicillin monotherapy group; \( P = .49 \). After weighting was applied, patients in both treatment groups were similar with regards to underlying characteristics, including baseline renal function.

Time to Clearance
The median time to blood culture clearance was 2.56 days (61.5 hours) in the combination therapy arm and 2.98 days (71.5 hours) in the monotherapy arm (Table 2). After additional adjustment for removal of central venous catheters and drainage of intra-abdominal collections within 72 hours of the time the first blood positive culture was obtained in the propensity-weighted cohort, patients receiving combination therapy experienced clearance 0.42 days (10 hours) faster than children receiving ampicillin monotherapy (adjusted mean difference 0.42; confidence interval (CI), .02 to .82; \( P = .04 \)).
Bacteremic Relapse

There were 54 children who experienced bacteremic relapse; 27 (17%) in the combination therapy group and 27 (18%) in the ampicillin monotherapy arm. Adjusting for source control at any time during the antibiotic treatment course, there was no difference in the risk of bacteremic relapse between the treatment groups (adjusted hazards ratio [aHR] 1.12; 95% CI, .65 to 1.92).

The median time to relapse was 21 days after antibiotic therapy was discontinued. Patients who did not have their central line removed at any time during their treatment course, regardless of their treatment group, were approximately 2.5 times more likely to experience a subsequent relapse compared to patients who underwent catheter removal (aHR 2.60; 95% CI, 1.04 to 6.46).

Acute Kidney Injury

There were 30 (18%) and 14 (9%) patients in the combination group and ampicillin monotherapy groups, respectively, who experienced renal risk, injury, or failure during their treatment course. Of those children receiving low-dose gentamicin, the median duration of therapy with this agent was 9.6 days. Patients receiving low-dose gentamicin had about twice the risk of developing AKI compared to patients who did not receive this agent (HR 2.01; 95% CI, 1.29–3.54). This estimate was slightly attenuated after adjusting for the receipt of additional nephrotoxins (aHR 1.94; 95% CI, 1.48–2.97). The median time to AKI development was 6.4 days. For each additional nephrotoxic agent received, the risk of developing AKI increased by 63% (HR 1.63; 95% CI, 1.24–2.14). After adjusting for the number of additional nephrotoxic agents received in each group, combination therapy remained associated with an increased risk of subsequent AKI (HR 2.29; 95% 2.14–8.63).

DISCUSSION

The role of aminoglycoside therapy in the treatment of enterococcal bacteremia in the absence of cardiac valve involvement is
evaluated in children. Prolonged-course low-dose gentamicin has not been previously studied. Similar data evaluating the role of either short-course or prolonged-course low-dose gentamicin developing renal dysfunction, respectively [12].

In our cohort, children who received low-dose gentamicin in combination with ampicillin had almost twice the risk of developing AKI, compared to patients receiving ampicillin monotherapy for E. faecalis bacteremia, even after adjustment was made for the receipt of additional nephrotoxins.

We did not evaluate long-term nephrotoxicity associated with synergistic gentamicin, and it is unclear whether AKI associated with low-dose gentamicin contributes to “multifactorial” causes of chronic renal failure later in life. The implications of aminoglycoside-induced AKI on long-term renal function warrant further study. Some additional disadvantages associated with the routine use of low-dose gentamicin include (1) discomfort and burden associated with frequent catheter access (placing children at risk for subsequent infections); (2) blood withdrawal for therapeutic drug monitoring; (3) aminoglycoside drug acquisition, preparation, and administration costs; and (4) clinical pharmacists’ compensation for therapeutic drug monitoring calculations. Of the 30 children receiving combination therapy who developed AKI, only 12 children received therapeutic drug monitoring, making it difficult to make any conclusions about the need for therapeutic drug monitoring for children receiving low-dose gentamicin as an early predictor of AKI.

This study has some limitations. As less than 10% of children in our cohort received low-dose gentamicin for 5 or less days, we were unable to evaluate the potential role for shorter-courses of low-dose gentamicin. Similarly as no patients received once-daily aminoglycosides, we were unable to evaluate the role of

<table>
<thead>
<tr>
<th>Duration of bacteremia, days (mean, standard deviation)</th>
<th>Ampicillin and Gentamicin</th>
<th>Ampicillin</th>
<th>Point Estimate; 95% CI</th>
<th>P Value</th>
<th>Weighted Sample</th>
<th>Weighted Sample With Additional Adjustmenta</th>
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</thead>
<tbody>
<tr>
<td>Duration of bacteremia, days (mean, standard deviation)</td>
<td>2.56 (1.82)</td>
<td>2.98 (1.43)</td>
<td>Mean difference: 0.40; −.01 to .80</td>
<td>.06</td>
<td>Mean difference: 0.42; .02 to .82</td>
<td>.04</td>
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<tr>
<td>Bacteremic Relapse</td>
<td>27 (16.6%)</td>
<td>27 (18.0%)</td>
<td>HR: 1.14; .66 to 1.98</td>
<td>.65</td>
<td>HR: 1.12; .65 to 1.92</td>
<td>.68</td>
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<tr>
<td>Acute Kidney Injury</td>
<td>30 (18.4%)</td>
<td>14 (9.3%)</td>
<td>HR: 2.01; 1.29 to 3.54</td>
<td>.04</td>
<td>HR: 1.94; 1.48 to 2.97</td>
<td>.01</td>
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<td>Risk; n (percent)b</td>
<td>16 (64.0%)</td>
<td>9 (36.0%)</td>
<td>HR: 1.14; .66 to 1.98</td>
<td>.65</td>
<td>HR: 1.12; .65 to 1.92</td>
<td>.68</td>
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<tr>
<td>Injury</td>
<td>12 (85.7%)</td>
<td>2 (14.3%)</td>
<td>HR: 2.01; 1.29 to 3.54</td>
<td>.04</td>
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<td>.01</td>
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<tr>
<td>Failure</td>
<td>2 (40.0%)</td>
<td>3 (60.0%)</td>
<td>HR: 2.01; 1.29 to 3.54</td>
<td>.04</td>
<td>HR: 1.94; 1.48 to 2.97</td>
<td>.01</td>
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Abbreviations: CI, confidence interval; HR, hazard ratio.

a Additional adjustment for potential confounders was performed for each outcome as follows: Duration of bacteremia (mean, standard deviation): central line removal and drainage of intra-abdominal abscesses within 72 hours of the time first positive blood culture was obtained; Bacteremic relapse: central line removal and drainage of intra-abdominal abscesses at any time during antibiotic treatment course; Acute kidney injury: Receipt of intravenous contrast or at least 48 hours of any of the following medications as a dichotomous variable: amphotericin, colistin, cyclosporine, acyclovir, vancomycin, cidofovir, cyclophosphamide, methotrexate, cisplatin, or nonsteroidal anti-inflammatory drugs.

*b For the risk, injury, and failure categories of acute kidney injury, percentages compare the number of patients in the ampicillin and low-dose gentamicin groups and the ampicillin monotherapy groups.

The safety of low-dose gentamicin has been evaluated in adults receiving a 2-week course of gentamicin for methicillin-susceptible S. aureus (MSSA) endocarditis [18]. Adult patients receiving 2 weeks of low-dose gentamicin in combination with nafcilin experienced more renal impairment than patients receiving nafcilin alone leading the investigators to conclude that gentamicin should only be considered for the first 3–5 days of therapy for MSSA endocarditis [18]. It was subsequently shown, however, in a study of 236 adult patients with S. aureus bacteremia and native valve endocarditis that even 3–5 days of low-dose gentamicin developing the risk of AKI with 22% and 8% in the groups that did and did not receive low-dose gentamicin developing renal dysfunction, respectively [12]. Similar data evaluating the role of either short-course or prolonged-course low-dose gentamicin has not been previously evaluated in children.

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This study has some limitations. As less than 10% of children in our cohort received low-dose gentamicin for 5 or less days, we were unable to evaluate the potential role for shorter-courses of low-dose gentamicin. Similarly as no patients received once-daily aminoglycosides, we were unable to evaluate the role of...
this strategy as a potential alternative to intermittent low-dose gentamicin. When adjusting for the use of nephrotoxins (in addition to aminoglycosides), we included 10 commonly prescribed nephrotoxins, as well as intravenous contrast. As this was not an exhaustive list, we realize that some patients may have received additional nephrotoxins we did not account for. Additionally, evaluating treatment effects from observational data can be problematic as prognostic factors may influence treatment decisions. We attempted to overcome this potential selection bias with the inclusion of propensity scores weighting. With the use of propensity scores, we were able to achieve adequate balance of measured baseline variables. As with all observational studies, we cannot rule out residual confounding by unmeasured variables related to disease severity. However, our final model demonstrated minimal residual confounding that would have been unlikely to change our estimate of the association between combination therapy and our clinical outcomes. Despite these limitations, we believe our results suggest that low-dose gentamicin for the treatment of uncomplicated enterococcal bacteremia can pose harm to children with limited benefit.

Notes

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