

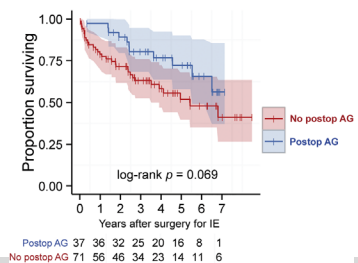
Aminoglycosides For Surgically Treated Enterococcal Endocarditis

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Aminoglycosides are a mainstay of treatment for enterococcal infective endocarditis. However, the benefit of adding aminoglycosides to cell wall-active agents after surgery is unclear. The aim of this study was to determine if adjunctive aminoglycoside treatment after surgery for enterococcal endocarditis leads to better outcomes. We included patients who underwent surgery for enterococcal endocarditis at our institution between July 2007 and July 2014. Treatment was defined as at least 1 dose of an aminoglycoside after surgery. Propensity to receive aminoglycosides was calculated in a model that included age, native vs prosthetic valve endocarditis, chronic kidney disease, high-level aminoglycoside resistance, metastatic infection, invasive disease, positive valve culture, and creatinine on the day of surgery. A multivariable Cox proportional hazards model was used to compare the primary outcome of death, adjusted for propensity to receive aminoglycosides, among patients who did and did not receive aminoglycosides. A total of 108 patients were identified of whom 37 (34%) received at least 1 dose of an aminoglycoside after surgery, with a median duration of 5 days (interquartile range: 2.5-10). In the multivariable model, patients treated with adjunctive aminoglycoside therapy had better survival than those treated with a cell wall-active agent alone, although the difference did not reach statistical significance (hazard ratio = 0.65, 95% CI: 0.32-1.33). The survival difference was consistently present in subgroups stratified by all-purpose refined diagnosis-related group mortality risk, and with varying definitions of aminoglycoside therapy. In conclusion, antibiotic monotherapy with a cell wall-active agent after surgery for enterococcal endocarditis may be inferior to combination therapy including an aminoglycoside.

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Unadjusted survival curves of patients treated with and without adjunctive aminoglycoside.

Central Message

In patients with enterococcal endocarditis, antibiotic monotherapy after surgery may be inferior to combination with an aminoglycoside.

Perspective Statement

The benefit of adjunctive aminoglycoside treatment after surgery for enterococcal endocarditis is unclear. We found that patients who received aminoglycosides after surgery seemed to have better survival compared to those who did not, even after adjusting for other factors that might vary between them.

See Editorial Commentary pages xx-xx.

Enterococcus is the third most common cause of infective endocarditis (IE), accounting for 10% of cases in most series.^{1,2} They are not considered very virulent organisms, but infections can be challenging to treat because of their inherent resistance to many antibiotics. In the 1940s, it was first noted that the use of penicillin alone in the treatment of enterococcal IE resulted in failure in as many as two-thirds of cases.^{3,4} Subsequently, the

combination of an aminoglycoside and penicillin was demonstrated to have synergy in vitro and improved clinical outcomes in several studies.^{3,5,6} Thus, for the past 5 decades, the recommended treatment for enterococcal IE has been a combination of a cell wall-active antimicrobial with an aminoglycoside for a minimum of 4-6 weeks in the absence of high-level aminoglycoside resistance.⁷⁻⁹ The optimal duration of aminoglycoside treatment has not been explored with randomized trials. Use of aminoglycosides carries significant risks including ototoxicity, which may be irreversible, and nephrotoxicity, which has been shown to occur even with short courses of aminoglycosides.¹⁰ Treatment is often prematurely discontinued or avoided altogether because of these adverse effects. In an effort to minimize exposure to aminoglycosides and their concomitant side effects, studies were conducted to

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assess outcomes with shorter duration of aminoglycoside treatment. Outcomes with shorter 2-week courses were comparable to the standard 4-6-week regimen.^{11,12} However, these included all patients with enterococcal IE without consideration of whether or not patients received surgical treatment. These days, a substantial proportion of patients with IE are treated surgically. With adequate source control achieved at surgery, treatment with a single antibiotic may be enough as is the standard practice for enterococcal infections at other sites, and there may be less need for treatment with antimicrobials that have significant potential for causing harm.

We designed this study to evaluate whether treatment with an aminoglycoside in addition to a cell wall-active antibiotic, leads to better outcomes in patients with surgically treated enterococcal IE, than treatment with a cell wall-active agent alone.

PATIENTS AND METHODS

Study Population

This was a retrospective cohort study that included patients who underwent surgery for enterococcal IE at Cleveland Clinic, a large multispecialty tertiary care referral center. Cases were identified from the Cleveland Clinic Infective Endocarditis Registry that includes all adult patients treated for IE at Cleveland Clinic. All patients older than 18 years who were operated on for enterococcal IE at Cleveland Clinic between July 1, 2007 and July 1, 2014 were screened for inclusion. All cases that met criteria for definite IE by Duke criteria were included.¹³ For patients who had multiple episodes of IE, only the first episode of surgically treated enterococcal IE was included. The study was approved by our institutional review board.

Data Collection

Data were collected through structured electronic queries and manual review of the electronic medical record. Information gathered included patient demographics, comorbid conditions, predisposing risk factors, echocardiographic findings, microbiologic data, histopathology, antibiotic treatment, and IE complications. Outcome variables including death, reoperation for IE, and serum creatinine were obtained. Mortality information was obtained from the electronic medical record and review of the Social Security Death Index, supplemented by publicly available data such as published obituaries.

Definitions

Enterococcus was identified as the causative microorganism of IE using previously published criteria.¹⁴

Invasive disease was defined as extension of the invasive process into the annulus or surrounding structures.¹⁵ High-level aminoglycoside resistance (HLAR) was defined according to the standards established by the National Clinical and Laboratory Standards Institute. HLAR implies that no synergy is expected from addition of the aminoglycoside. Preoperative aminoglycoside treatment was defined as receipt of at least 1 dose of an aminoglycoside before surgery. The duration of preoperative antimicrobials was not included owing to incomplete or missing data. Patients were classified according to whether they were treated with aminoglycosides after surgery. For the purpose of the primary analysis, aminoglycoside treatment was defined as receipt of at least 1 dose of an aminoglycoside after surgery.

Outcomes

The primary outcome was survival after surgical treatment of enterococcal IE. Secondary outcomes included relapse of enterococcal IE, reoperation for IE, and development of acute kidney injury (AKI). AKI was defined as $\geq 25\%$ increase in baseline creatinine concentration. The serum creatinine on the date of surgery was defined as the baseline serum creatinine. Patients with preexisting end-stage renal disease were excluded from analysis of the secondary outcome of AKI.

Statistical Analysis

Univariate comparisons between the 2 groups were made using Student *t*-test or Wilcoxon rank sum test for continuous variables and Pearson chi-square test or Fisher exact test for categorical variables. Logistic regression methods were used to determine the propensity to receive an aminoglycoside for each patient. The variables included in the propensity score calculation were age, chronic kidney disease, native valve endocarditis (NVE) vs prosthetic valve endocarditis, HLAR, metastatic infection, invasive disease, positive valve cultures for *Enterococcus* sp., and serum creatinine on the day of surgery. Univariable comparisons of survival estimates for the effect of adjunctive aminoglycoside treatment were generated using Kaplan-Meier curves. The strata were compared using the log rank test. Cox proportional hazard models were constructed to compare the primary outcome between patients treated with or without an aminoglycoside while controlling for sex, all-purpose refined diagnosis-related group (APR-DRG) mortality risk, and propensity to receive aminoglycosides. The resulting models were used to generate plots of the survival curves illustrating the differences in survival

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