Endocarditis Trends in the United States Demonstrate Increasing Rates of *Staphylococcus aureus*: 1999–2008

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INTRODUCTION

Estimates of the incidence and impact of bacterial infective endocarditis (IE) have been limited by the infrequency of the disease. Administrative data analyses can provide important information across a broad range of hospitals and regions. We used a recent, nationally representative sample to estimate the incidence of hospitalizations for bacterial IE in the United States.

METHODS

We conducted a retrospective cohort study using the 1999–2008 Nationwide Inpatient Sample (NIS), which is produced by the Agency for Healthcare Research and Quality. The NIS is the largest all-payer inpatient database in the United States (approximately 8 million records per year).[1] Admissions related to bacterial IE were identified by the presence of International Classification of Diseases, Ninth Edition codes 421.0, 421.1, 421.9 or 996.61, combining two previous strategies.[2, 3] The etiological agent of IE was determined by the presence of organism-specific infection (e.g. 041.x) and bacteremia codes (038.x). Incidence was estimated using the rate of IE-related discharges per 100,000 US population-years. Rates were calculated quarterly based on discharge date; the denominator was adjusted annually based on the US population. Trends in admission rate were evaluated using

joinpoint methods, allowing the trend to change over time.[4] We measured the effect of organism on in-hospital mortality using logistic regression, adjusted for age, gender, payer, and comorbidities. The dataset was constructed in SAS System, version 9.22; analyses were performed in Stata/IC, version 11.2 and Joinpoint Regression Program, version 3.4.3, using the stratification and weighting data provided with the NIS to create nationally-representative estimates. Additional detail on study methods is available in an online appendix.

RESULTS

Of the 78.2 million records in the 1999–2008 NIS, 93,511 met inclusion criteria. Using weights, these records correspond to457,690 discharges nationwide. After exclusion of 9,538 admissions ending in inpatient transfer and 273 (0.3%) with unknown disposition, the main study sample consisted of 83,700 discharges (409,665 weighted). Most episodes involved patients who were male (59.3%), white (71.4%), and insured by Medicare (57.2%). Of those discharges for which an organism was identified, staphylococci were most common (57.5%), followed by streptococci/enterococci (33.3%).

Between the first quarter of 1999 and the first quarter of 2006, the rate of bacterial IE-related hospitalizations increased from 11.4 per 100,000 population-years to 16.6 per 100,000 population-years (test of trend, $p < 0.001$). This trend corresponds to an average percent change (APC) of 1.1% per quarter (95% confidence interval (CI): 0.9% to 1.3%). After the first quarter of 2006, the rate stabilized, with an APC of 0.1% (95% CI: −0.6% to 0.8%). Substantial differences were evident in the rate of IE-related admissions caused by different organisms over the study period (Figure 1A). Admissions associated with staphylococcal IE grew at a rate of 1.1% per quarter (95% CI: 0.9% to 1.3%), rising from 3.3 to 5.4 cases per 100,000 person-years from first quarter 1999 to fourth quarter 2008 (test of linear trend, $p < 0.001$). Most of the increase in staphylococcal IE admissions was due to IE caused by *S. aureus*, which increased at a rate of 1.7% per quarter between first quarter 1999 and first quarter 2006 (95% CI: 1.3% to 2.0%). Interestingly, rates of *S. aureus*-associated IE stabilized between 2006 and 2008 (APC 0.1%, 95% CI: −1.1% to 1.2%).

We limited the cohort to 33,956 admissions(165,563 weighted) that occurred in 2002 or later, for which a etiologic organism was identified (excluding unknown organisms and unspeciated staphylococcus), and which had complete covariate data. Admissions for *S. aureus*-related IE were associated with higher probability of in-hospital mortality than streptococcal/enterococcal IE (17.5% versus 8.9%, $p < 0.001$). After adjustment, IE caused by *S. aureus* was associated with a 57.1% greater risk of in-hospital mortality (risk difference: 5.9% $p < 0.001$) when compared with streptococcal/enterococcal IE (Figure 1B).

DISCUSSION

This report estimates the current incidence and trends in hospitalizations due to bacterial IE in the United States at the beginning of the 21st Century. We found that the rate of IE-related hospitalizations grew markedly, and that this growth was driven primarily by increases in *S. aureus* IE. Patients with *S. aureus* IE were also more likely to die during the hospitalization. Since these findings were drawn from a representative sample of over 78 million hospitalizations, they are generalizable to contemporary medical practice.

Our finding that *S. aureus* is the predominant cause of IE in the 21st Century is consistent with results from the International Collaboration on Endocarditis.[3] Our results contrast with those of Tleyjeh and colleagues, who found no significant change in IE rates or etiology during 1970–2000 in Olmstead County, Minnesota.[5] The generalizability of that important

study was limited by its small size (107 IE cases during the 30 year time period), small geographic scope, and lack of racial and ethnic diversity. By contrast, the current investigation involved a nationally-representative sample of contemporary US admissions.

This investigation has important strengths. Our study design employs a large, contemporary, and nationally representative dataset. Such a dataset avoids referral bias,[6] ensures that our results are broadly generalizable, and allows for sufficient sample size for statistical inference. The study is limited by its use of ICD-9 diagnosis codes, which have been associated with both false positive and negative findings.[7] However, others have reported good agreement between IE diagnosis codes and clinical criteria obtained from medical records.[8] Our inability to access laboratory results resulted in a relatively high proportion of IE cases without organism identification (43.8%). However, the number of unidentified cases grew at a rate similar to that of identified cases (APC 1.1% versus 1.2%), suggesting that our findings are not due to improvements in coding.

Despite these limitations, our study is uniquely able to make a number of observations. We estimate the incidence of bacterial IE in the United States and document its increasing prevalence in the early 21st Century. This growth was attributed primarily to increased rates of IE related to *S. aureus*, which was associated with worse outcomes and higher costs compared to IE caused by other organisms.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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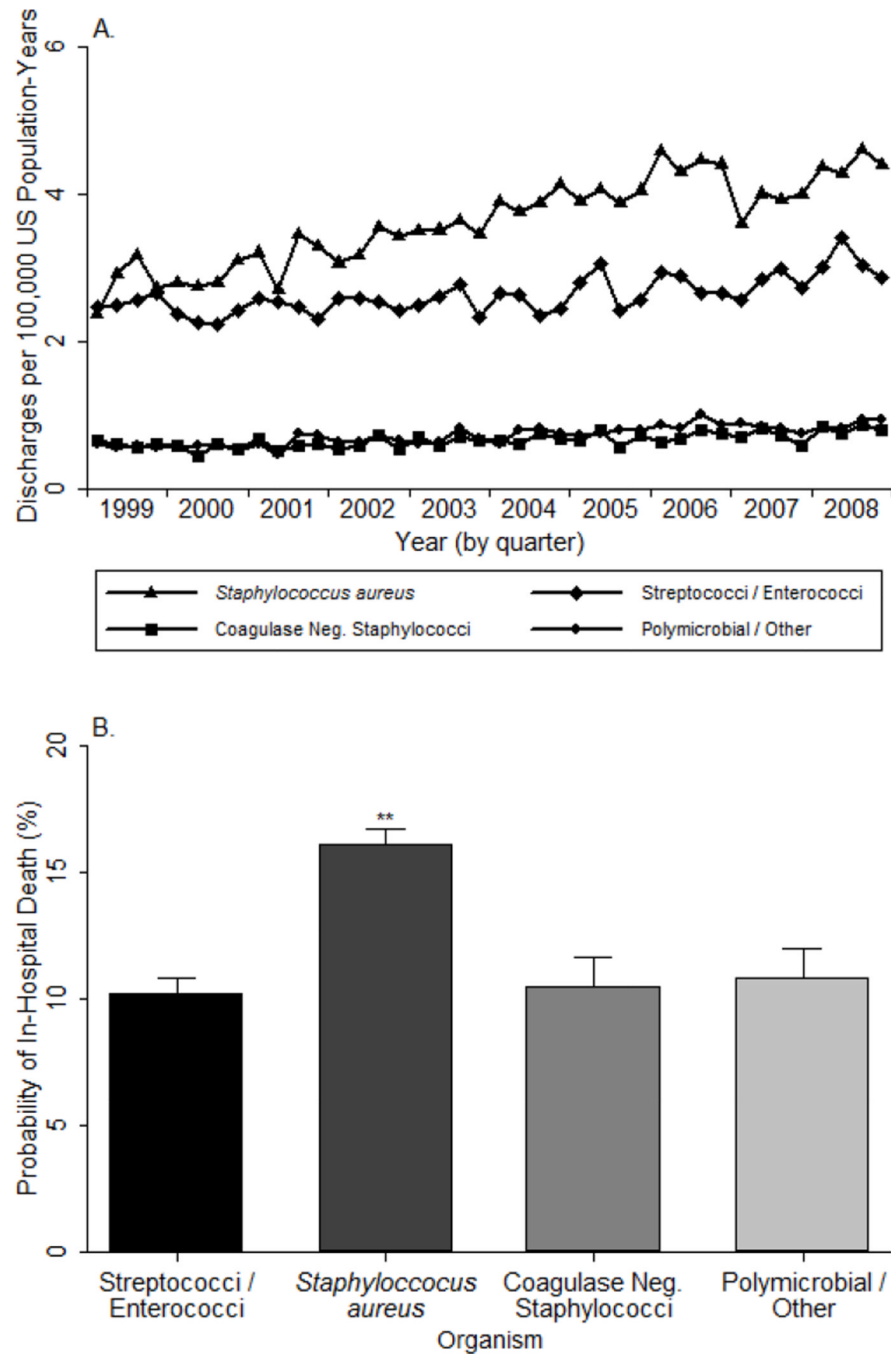
Figure 1.
(A) Temporal trend in the total rate of bacterial infective endocarditis-associated hospitalizations in the United States: 1999–2008; (B) Covariate-adjusted in-hospital mortality
** Significantly different from streptococci/enterococci at 0.1% level.