A matched prospective cohort study on *Staphylococcus aureus* and *Escherichia coli* bloodstream infections: Extended perspectives beyond resistance

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Background: Bacteremias caused by *Staphylococcus aureus* and *Escherichia coli* are among the most common bloodstream infections (BSIs) in adults. The aim of the study was to investigate risk factors for infection and clinical outcomes of bacteremias caused by *S aureus* or *E coli*.

Methods: We conducted a 1-year matched prospective cohort study including 150 patients with BSI caused by susceptible or resistant *S aureus* or *E coli* and 300 controls without BSI caused by these organisms.

Results: Of the 150 episodes of bacteremia, 37% were caused by *S aureus* (including 5 cases of methicillin-resistant *S aureus* [MRSA]) and 63% were caused by *E coli* (including 9 cases of extended-spectrum beta lactamase [ESBL]-producing *E coli*). We identified 4 independent risk factors for acquisition of *S aureus* bacteremia (emergency, peripheral or central vascular catheter, renal disease) and 6 risk factors for *E coli* bacteremia (emergency, peripheral or central vascular catheter, malignancy, cytoreductive or immunosuppressive therapy). Both types of bacteremia were associated with an increased length of hospital stay compared with controls. We observed a 5-fold increase in the 30-day mortality rate for bacteremias due to *S aureus,* and a 2-fold increase in BSI caused by *E coli*. The in-hospital mortality rate was increased by 6-fold for *S aureus* and by 3-fold for *E coli*.

Conclusion: Longer hospitalization periods and increased mortality of bacteremias caused by *S aureus* or *E coli*, irrespective of susceptibility, implicate controlling for risk factors at an early stage.

Key Words: Bacteremia; risk factor; mortality.

Staphylococcus aureus and *Escherichia coli* are the leading causes of gram-positive and gram-negative bacteremias, respectively. Both organisms are among the most commonly isolated pathogens in hospital- and community-acquired bloodstream infections (BSIs).[1-5] Bacteremias due to *S aureus* and *E coli* cause a clinically relevant infection in a high proportion of cases and are associated with high morbidity and mortality.[1,6-11] Treatment of patients with severe bacteremia and sepsis entails high costs.[10,11] Furthermore, treatment of such infections has become increasingly difficult due to the emergence of antimicrobial-resistant strains, including methicillin-resistant *S aureus* (MRSA) and extended-spectrum beta lactamase (ESBL)-producing *E coli*.[1,4,5] Thus, these organisms represent an increasingly important problem in clinical practice, as well as for the health care system as a whole.

S aureus bacteremias (SABs) and *E coli* bacteremias (ECBs) have been studied in various patient populations meeting selective criteria.[12-19] Notably, the investigation of bacteremias caused by MRSA and ESBL-producing *E coli* has become a major focus of interest over the past few years.[20-26] However, few studies have assessed risk factors for and clinical outcomes of BSI caused by *S aureus* or *E coli* strains irrespective of their antimicrobial susceptibility. Most of these studies were performed in nonmatched settings.[27-34] There is even less information about clinically relevant parameters of SABs or ECBs in a general, nonspecific patient population without selection criteria.[35] The present study was designed and conducted as a matched prospective cohort study investigating bacteremias caused by susceptible or resistant strains of *S aureus* or *E coli* in

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Conflicts of interest: None to report.

0196-6553/$36.00

doi:10.1016/j.ajic.2010.04.212

a nonselected cohort of adult patients, including patients of all specialities or underlying preexisting conditions. The present study investigated risk factors for infection and clinical outcomes of bacteremias caused by susceptible or resistant strains of *S aureus* or *E coli* at an Austrian tertiary care center by analyzing the following outcome variables: total and postinfectious length of hospital stay (LOS), 30-day mortality, and overall in-hospital mortality.

METHODS

Setting

This study was performed at the Vienna General Hospital, a 2137-bed tertiary care university teaching hospital in Vienna, Austria. The hospital has 1875 standard care beds and 262 intensive care and intermediate care beds. It provides specialized medical and surgical care, including hematopoietic stem cell and solid organ transplantation, for an average of 99,000 inpatients (98,615 in 2007) and 1,290,000 outpatients (1,289,806 in 2007).

Study design

This was a matched prospective cohort study matching cases and controls at a ratio of 1:2 over a 1-year period. Adult patients (age $>$18 years) with a positive blood culture for either *E coli* or *S aureus* between July 1, 2007 and June 30, 2008 were included in the study as "case patients." Each was matched with two patients ("control patients") without a BSI caused by *S aureus* or *E coli*. Invasive infections of controls caused by organisms other than *S aureus* or *E coli* were acceptable but not required for inclusion. Control patients had to be admitted to the same ward on the same day ($\pm$2 days) as the case patients. The time when the first positive blood culture sample was obtained was chosen as the time of inclusion into the study. The Medical University of Vienna's Institutional Review Board and Ethical Committee approved the study design.

Data collection

The following data were collected prospectively for both case and control patients from medical records: patient characteristics (age, sex, and location at the onset of the BSI), clinical conditions (admission diagnosis, comorbidities, type of admission, frequent exposure to health care institutions, ongoing cytoreductive/immunosuppressive therapy, presence of invasive medical devices, antimicrobial pretreatment and surgical interventions before enrollment into the study), characteristics of the bacteremia (type of BSI, site of infection, source of acquisition). Outcomes of interest included total LOS, postinfectious LOS, in-hospital mortality, and death within 30 days after enrollment into the study.

Definitions

SAB was defined as retrieval of *S aureus* in at least one blood culture specimen. ECB was defined as the presence of at least one positive blood culture for *E coli*. All positive blood cultures were categorized as true or contaminant based on the clinical history, physical findings, clinical course, and response to treatment. Infections with the first positive blood culture within 48 hours of admission were considered community-acquired. Nosocomial infections were defined as (1) infections occurring more than 48 hours after admission to the hospital, (2) infections occurring less than 48 hours after admission in patients who had been hospitalized during the previous 2 weeks, or (3) infections occurring less than 48 hours after admission in patients who had been transferred from another hospital or a nursing home, according to criteria proposed by the Centers for Disease Control and Prevention.[36] Total LOS was defined as the period between admission and discharge. Postinfectious LOS was defined as the period between enrollment and discharge. In-hospital mortality was defined as any death occurring in the hospital, and 30-day-mortality was defined as any death occurring within 30 days after enrollment into the study.

Microbiological methods

All microbiological specimens were processed at the Vienna General Hospital's Division of Clinical Microbiology. For all blood cultures, approximately 10 mL of blood was inoculated each into aerobic and anaerobic bottles of a commercially available blood culture system (Vital; bioMeriéux, Marcy l'Étoile, France) and incubated for 7 days at 35.5°C. Isolates were identified by standard microbiological methods. Antimicrobial susceptibility testing was performed according to Clinical and Laboratory Standards Institute guidelines.[37] Kirby-Bauer disk-diffusion results were supplemented by testing minimum inhibitory concentrations (E-Test; Biodisk, Solna, Sweden) whenever necessary.

Statistical analysis

For comparison of demographic and clinical characteristics of cases and controls, the χ^2 test was used for categorical parameters and Fisher's exact test was used when fewer than 5 observations per cell were present. Wilcoxon's two-sample test was used for metric variables. For analyzing the case-control study, a conditional logistic regression with backward selection of relevant parameters was performed. Age, sex, LOS before enrollment, frequent exposure to health care institutions, type of admission (elective vs emergency), need for