International Journal of Infectious Diseases 37 (2015) 129–134

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Nosocomial Gram-negative bacteremia in intensive care: epidemiology, antimicrobial susceptibilities, and outcomes

Wendy Irene Sligl [a,*], Tatiana Dragan [b], Stephanie Wrenn Smith [c]

[a] Divisions of Critical Care Medicine and Infectious Diseases, Faculty of Medicine and Dentistry, University of Alberta, 2–124 Clinical Sciences Building, 8440-112 Street, Edmonton, AB, T6G 2B7, Canada
[b] Department of Medical Microbiology and Immunology, Faculty of Medicine and Dentistry, University of Alberta, Edmonton, Alberta, Canada
[c] Division of Infectious Diseases, Faculty of Medicine and Dentistry, University of Alberta, Edmonton, Alberta, Canada

ARTICLE INFO

Article history:
Received 20 April 2015
Received in revised form 3 June 2015
Accepted 28 June 2015

Corresponding Editor: Eskild Petersen, Aarhus, Denmark

Keywords:
Bacteremia
Gram-negative
Critical care
Intensive care
Nosocomial infection
Antimicrobial resistance

SUMMARY

Objectives: To describe the epidemiology, antimicrobial susceptibilities, treatment, and outcomes of intensive care unit (ICU)-acquired Gram-negative bacteremia.
Methods: Patients with ICU-acquired Gram-negative bacteremia from 2004 to 2012 were reviewed retrospectively. Independent predictors of mortality were examined using multivariable Cox regression.
Results: Seventy-eight cases of ICU-acquired Gram-negative bacteremia occurred in 74 patients. The infection rate was 0.97/1000 patient-days. Mean patient age was 55 years, 62% were male. The most common admission diagnoses were respiratory failure (34%) and sepsis/septic shock (45%). Mortality was 35% at 30 days. The most common source of bacteremia was pneumonia (33%). Of 83 Gram-negative isolates, *Escherichia coli* (20%) and *Pseudomonas aeruginosa* (18%) were most common. For aerobic isolates, susceptibilities to ciprofloxacin (61%) and piperacillin/tazobactam (68%) were low. For pseudomonal isolates, susceptibilities to ciprofloxacin (53%), piperacillin/tazobactam (67%), and imipenem (53%) were equally disappointing. Adequate empiric antimicrobial therapy was prescribed in 85% of bacteremia cases. On multivariable analysis, adequate empiric therapy (adjusted hazard ratio (aHR) 0.38, 95% confidence interval (CI) 0.16–0.89), immune suppression (aHR 3.4, 95% CI 1.4–8.3), and coronary artery disease (aHR 4.5, 95% CI 1.7–11.9) were independently associated with 30-day mortality.
Conclusions: ICU-acquired Gram-negative bacteremia is associated with high mortality. Resistance to ciprofloxacin, piperacillin/tazobactam, and carbapenems was common. Coronary artery disease, immune suppression, and inadequate empiric antimicrobial therapy were independently associated with increased mortality.

1. Introduction

Despite considerable preventative efforts, hospital-acquired infections continue to contribute to substantial morbidity and mortality,[1] occurring in approximately 4% of hospitalized patients.[2] An estimated 250 000 nosocomial bloodstream infections occur each year in the USA,[3] with approximately 30% due to Gram-negative bacilli. Mortality rates in Gram-negative sepsis are high, and can be up to 50% depending on patient factors, as well as timing and appropriateness of empiric antimicrobial therapy.[4–7]

Although intensive care units (ICUs) account for less than 10% of the total number of beds in most hospitals, more than 20–30% of all nosocomial infections are acquired in the ICU,[2,8] with high rates of antimicrobial resistance[9,10] and mortality[7,11] when compared with the general hospital population. Understanding the local epidemiology and antimicrobial susceptibility patterns in ICU-acquired Gram-negative bacteremia may facilitate the development of empiric therapy guidelines, formulary restrictions, and/or antimicrobial stewardship programs, resulting in improved patient outcomes.

The aim of this study was to provide up-to-date data on the epidemiology (including incidence, source, microbial etiology, antimicrobial susceptibilities, and outcomes) of nosocomial Gram-negative bacteremia in a population of critically ill patients. A comparison of rates, microbiology, antimicrobial susceptibilities,

* Corresponding author. Tel.: +1 780-492-8311; fax: +1 780-492-1500.
E-mail address: wsligl@ualberta.ca (W.I. Sligl).

http://dx.doi.org/10.1016/j.ijid.2015.06.024

and appropriateness of empiric therapy over time was also performed, in particular a comparison to data published previously from the same patient population.[12]

2. Materials and methods

A retrospective observational cohort study was conducted at the University of Alberta Hospital, a 650-bed academic quaternary care referral hospital in Edmonton, Canada and the principal teaching hospital of the University of Alberta, Faculty of Medicine and Dentistry. It is a level-one trauma center, the largest solid organ transplantation center in Western Canada, and has a referral area of over two million.

The University of Alberta Hospital contains a 32-bed adult general systems ICU that admits general medical, surgical, trauma, and solid organ transplant patients. The ICU provides general invasive hemodynamic monitoring and support, mechanical ventilation, and renal replacement therapy, as well as extracorporeal liver support. Other specialized support therapies such as extracorporeal membrane oxygenation (ECMO) are provided in the cardiovascular ICU.

This study was conducted as part of a quality improvement study through Infection Prevention and Control and was therefore exempt from ethics submission as per the Research Ethics Board at the University of Alberta. Infection Prevention and Control (IPC) monitors all inpatient populations prospectively, including ICU patients, for the development of nosocomial infection(s). Positive blood cultures are identified by the clinical microbiology laboratory (BACTEC 9240 Blood Culture System; Becton Dickinson Biosciences) and reviewed by IPC daily. Charts are subsequently reviewed and blood culture isolates categorized as contaminants, community-acquired, or nosocomial using standardized US Centers for Disease Control and Prevention/National Healthcare Safety Network (CDC/NHSN) criteria.[13] For nosocomial bacteremia, the originating source is then identified and subcategorized.

All cases of ICU-acquired Gram-negative bacteremia from January 1, 2004 to December 31, 2012 were reviewed. Demographic data, the source of bacteremia, causative microorganisms, antimicrobial susceptibilities, choice of empiric antibiotic therapy, ICU and hospital lengths of stay (LOS), and 30-day mortality rates were collected. Data were subsequently compared to previously published data for the period 1999–2003 in the same patient population.[12]

Immune compromise was defined as chronic steroid use (daily equivalent of 20 mg prednisone for $\geq$1 month per year), solid organ or hematopoietic stem cell transplantation, receipt of chemotherapy within the previous month, neutropenia (absolute neutrophil count $<1.0 \times 10^9$ cells/L) at the time of admission, or HIV/AIDS (CD4 count <200 cells/μl). End-stage renal disease (ESRD) was defined as kidney failure necessitating either peritoneal or intermittent hemodialysis prior to admission. Empiric therapy was deemed effective if treatment was with an agent to which the microorganism was ultimately susceptible. Multi-drug resistance in *Pseudomonas* species was defined as resistance to three or more first-line antimicrobials in the following classes: β-lactams, carbapenems, aminoglycosides (AGs), and fluoroquinolones.

2.1. Statistical analysis

Epidemiological data were reported, including descriptive statistics such as proportions, percentages, means, and medians. Characteristics of subjects who died and survived were compared using the *t*-test or Mann–Whitney *U*-test (as appropriate based on their distribution) for continuous variables. The Chi-square test or Fisher's exact test was used for categorical variables.

Kaplan–Meier survival curves were then constructed and log-rank tests performed for variables associated with mortality on univariate analysis.

Multivariable Cox regression modeling was subsequently performed to identify variables independently associated with 30-day mortality. The APACHE II score (Acute Physiology and Chronic Health Evaluation) was included for clinical significance. Otherwise variables identified to be significantly associated with increased mortality ($p < 0.1$) on univariate analysis were entered into the model. There were no proportional hazards violations, which were tested using time covariate interaction terms. Results are presented as adjusted hazard ratios (aHR) and 95% confidence intervals (CI). All statistical tests were two-sided and *p*-values of <0.05 were considered statistically significant.

Statistical analyses were performed using IBM SPSS Statistics for Windows, version 22.0 (IBM Corp., Armonk, NY, USA).

3. Results

There were 11 602 admissions to the general systems ICU from January 1, 2004 to December 31, 2012. A total of 78 episodes of ICU-acquired Gram-negative bacteremia occurred in 74 patients, resulting in an overall infection rate of 6.7 per 1000 ICU admissions, or 9.7 per 10 000 patient-days. These rates are similar to those observed in the previous study (6.9 per 1000 ICU admissions and 11.3 per 10 000 patient-days). Annual infection rates fluctuated by year from 1.6 to 9.6 per 1000 admissions and 2.3 to 15.0 per 10 000 patient-days, consistent with expected year-to-year variation.

The mean patient age was 55 years (range 18–85, standard deviation (SD) 15.8 years) and 46/74 (62.2%) were male. A large number of patients (26/74, 35%) were immune compromised. Additional specific patient demographics can be found in Table 1.

The majority of patients were admitted with medical diagnoses (51/72, 69%). Admitting diagnoses included respiratory failure (25/74, 34%), sepsis or septic shock (33/74, 45%), liver transplantation (7/74, 10%), and trauma/major burns (5/75, 7%). The mean APACHE II score was 25 (SD 8.3) at the time of admission, and 73/78 (94%) patients required invasive mechanical ventilation.

The most common source of bacteremia was pneumonia, in 26/78 (33%) patients, as was observed in the previous study. Other common sources included gastrointestinal tract infections (not endoscopy-related) (17/78, 22%) and catheter-related bloodstream infections (10/78, 13%) (Figure 1). A decrease in catheter-related bloodstream infections was observed from 1999–2003 to 2004–2012 (22% vs. 13%, respectively).

Bacterial species identified can be found in Figure 2. In summary, the most common bacterial pathogen was *Escherichia coli* (17/83, 21%), followed by *Pseudomonas aeruginosa* (15/83, 18%) and *Klebsiella* species (13/83, 16%).

The majority of isolates were aerobic Gram-negative bacilli (71/83, 86%), of which 49/83 (59%) were *Enterobacteriaceae*. Glucose non-fermenting organisms (Pseudomonas and Stenotrophomonas) accounted for 21/83 (25%) cases of bacteremia.

Multidrug-resistant (MDR) pathogens were isolated in 14/83 (17%) cases, including extended-spectrum β-lactamase producers (ESBLs; 5/83, 5%), carbapenem-resistant *Enterobacteriaceae* (CRE; 2/83, 2%), and MDR Pseudomonas (7/83, 8%).

The majority of infections were monomicrobial (63/78, 81%). In 15 polymicrobial infections, three were with another Gram-negative organism, 10 with Gram-positive organisms, and there were two events in which additional Gram-negative and Gram-positive organisms were identified.

Overall aerobic Gram-negative and pseudomonal susceptibilities are shown in Table 2. Of all aerobic isolates tested, susceptibilities to ciprofloxacin (40/66, 61%) and piperacillin/tazobactam (44/65, 68%) were low. Similar numbers were observed