Predictive scoring model of mortality in Gram-negative bloodstream infection

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Abstract

Mortality is a well-recognized complication of Gram-negative bloodstream infection (BSI). The aim of this study was to develop a model to predict mortality in patients with Gram-negative BSI by using the Pitt bacteraemia score (PBS) and other clinical and laboratory variables. A cohort of 683 unique adult patients who were followed for at least 28 days after admission to Mayo Clinic Hospitals with Gram-negative BSI from 1 January 2001 to 31 October 2006 and who received clinically predefined appropriate empirical antimicrobial therapy was retrospectively identified. Multivariable logistic regression was used to identify independent risk factors for 28-day all-cause mortality. Regression coefficients from a multivariable model were used to develop a risk score to predict mortality following Gram-negative BSI. Malignancy (OR 3.48, 95% CI 1.94–6.22), liver cirrhosis (OR 5.42, 95% CI 2.52–11.65), source of BSI other than urinary tract or central venous catheter infection (OR 5.54, 95% CI 2.42–12.69), and PBS (OR 1.98, 95% CI 0.92–4.25 for PBS of 2–3 and OR 6.42, 95% CI 3.11–13.24 for PBS ≥ 4) were identified as independent risk factors for 28-day mortality in patients with Gram-negative BSI. A risk-score model was created by adding points for each independent risk factor, and had a *c*-statistic of 0.84. Patients with risk scores of 0, 4, 8, 12 and 16 had estimated 28-day mortality rates of approximately 0%, 3%, 14%, 45%, and 81%, respectively. The Gram-negative BSI risk score described herein estimated mortality risk with high discrimination in patients with Gram-negative BSI who received clinically adequate empirical antimicrobial therapy.

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Introduction

The outcome of patients with Gram-negative bloodstream infection (BSI) depends on multiple host-related and pathogen-related factors. Acute severity of illness scores, such as the Acute Physiology and Chronic Health Evaluation (APACHE) score, are mostly used in critically ill patients who are admitted to intensive-care units (ICUs) [1]. However, the majority of patients with Gram-negative BSI do not require ICU admission [2]. Moreover, many of the variables used in such complex scores are not pertinent to Gram-negative BSI. The Pitt bacteraemia score (PBS), in contrast, has been used to stratify patients with BSI according to acute severity of illness. It is a simple score that is calculated at the time of initial patient evaluation by using temperature (1 point for temperature of 35.1–36°C or 39.0–39.9°C and 2 points for temperature of ≤ 35°C or ≥ 40°C), blood pressure (2 points for hypotension), mental status (1 point for disorientation, 2 points for stupor, and 4 points for coma), and the presence or absence of mechanical ventilation (2 points) and cardiac arrest (4 points) [3,4]. The PBS has been recently described as being superior to other acute severity of illness scores in predicting the outcome of patients with sepsis [5]. However, clinical variables other than acute severity of illness have been

associated with mortality following Gram-negative BSI, such as primary source of infection and patients' underlying medical conditions [6–13].

In this retrospective cohort study, clinical predictors of 28-day all-cause mortality following Gram-negative BSI in adult hospitalized patients were identified. The aim of the study was to develop a scoring model with which to estimate the risk of mortality following Gram-negative BSI by using the PBS and other clinical and laboratory variables that were independently associated with mortality.

Methods

Setting

The study was conducted at two Mayo Clinic hospitals: Saint Mary's Hospital and Rochester Methodist Hospital, located in Rochester, Minnesota. Both are large tertiary-care hospitals that combine to provide over 1950 licensed beds and care for local residents as well as referral patients in a wide variety of medical and surgical subspecialties.

Case definition

Gram-negative BSI was defined as the growth of any aerobic Gram-negative bacillus in a blood culture. The primary source of BSI was defined according to the CDC criteria [14]. Immunocompromised hosts were defined as patients with any of the following conditions: neutropenia, recent chemotherapy, treatment with corticosteroids, human immunodeficiency virus infection, recipients of solid organs or bone marrow transplants, or recipients of other immunosuppressive medications. Patients with cancer were defined as those with a current diagnosis of malignant tumour, excluding skin basal and squamous cell carcinoma.

Case ascertainment

A cohort of 708 patients with first episodes of monomicrobial Gram-negative BSI from 1 January 2001 to 31 October 2006 was retrospectively identified from the Mayo Clinic microbiology laboratory database. The detailed case ascertainment methods, as well as inclusion and exclusion criteria for enrolment in this cohort, have been described previously [2]. Briefly, we included adult patients $\geq$18 years of age with first episodes of monomicrobial BSI caused by aerobic Gram-negative bacilli. Included patients were hospitalized at any medical or surgical floor unit or ICU. All patients included in this cohort received what was predefined clinically as appropriate empirical antimicrobial therapy for Gram-negative BSI within 24 h of initial presentation. This included β-lactam antibiotics with activity against aerobic Gram-negative bacilli, such as β-lactam/β-lactamase inhibitors, third-generation and fourth-generation cephalosporins, a monobactam, and carbapenems with or without fluoroquinolones. Aminoglycoside regimens were excluded to avoid potential interaction with serum creatinine.

Statistical analysis

The primary objective was to determine clinical predictors of 28-day all-cause mortality in patients with Gram-negative BSI. We included in the analysis only patients who were followed for at least 28 days from the onset of Gram-negative BSI (n = 683). Patients who were lost to follow-up within 28 days of BSI were excluded from the analysis (n = 25). Death was confirmed by reviewing medical records and the Minnesota death registry database.

Multivariable logistic regression was used to analyse 28-day mortality. The following variables were considered as candidate predictors of mortality: age, gender, diabetes mellitus, congestive heart failure, chronic pulmonary disease, dementia, end-stage renal disease, liver cirrhosis, malignancy, immunocompromised state, PBS, primary source of BSI, infection site of acquisition, serum creatinine, and peripheral white blood cell (WBC) count. The primary source of BSI was dichotomized into urinary or central venous catheter (CVC)-related vs. other sources of BSI. This was based on the results of previous studies demonstrating that Gram-negative BSI secondary to a urinary tract or CVC infection was associated with better outcomes than BSI resulting from other sources of infection [6–13].

The functional form of each of the continuous variables was assessed. A generalized additive plot of the log odds of 28-day mortality (logit of probability) against a smoothed version of each continuous variable was used to gain a sense of linearity of their relationship. A smoothing spline of four degrees of freedom to characterize the continuous variable in the generalized additive model producing the plot was used. The final functional form of the variable was then formally tested in a logistic model.

To determine a final multivariable model on which the risk score would be based, bootstrap resampling was used. A model was derived in each bootstrap sample by applying the same backward model selection criteria (entry $p < 0.15$ and retention $p < 0.05$) every time, thus accounting for uncertainty in the model selection technique itself. The frequency of selected variables was computed as a percentage across all 400 bootstrap samples. The final multivariable prediction model contained all variables that were individually retained in at least 70% of the bootstrap samples.

The probability of concordance, or c-statistic, was used to quantify the discriminative ability of the final multivariable