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Factors associated with in-hospital mortality among critically ill surgical patients with multidrug-resistant Gram-negative infections

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ABSTRACT

Purpose: Multidrug-resistant (MDR) Gram-negative infection increases risk of mortality, other complications, and costs. The objective of this study was to determine the prevalence of and identify factors associated with in-hospital mortality among critically ill surgical patients.
Materials and methods: This case-control study included critically ill surgical patients from 2011 to 2014 who had a carbapenem-resistant Enterobacteriaceae (CRE), MDR *P. aeruginosa*, or MDR *Acinetobacter* spp. infection. Characteristics of patients surviving to hospital discharge were compared to those of non-survivors.
Results: Sixty-two patients were included. Of these, 21 (33.9%) died prior to discharge. Vasopressors and mechanical ventilation prior to index culture were more common in non-survivors vs. survivors (76.2% vs. 46.3%, $p = 0.03$; and 100% vs. 63.4%, $p = 0.001$). ICU and hospital LOS prior to index culture was longer in non-survivors vs. survivors (median 19 vs. 4 days, $p = 0.001$; and median 25 vs. 7 days, $p = 0.009$). In multivariate logistic regression, achievement of source control was the only variable associated with decreased in-hospital mortality [0.04 (95% CI 0.003–0.52); $p = 0.01$].
Conclusions: MDR Gram-negative infection is associated with significant in-hospital mortality among critically ill surgical patients. Source control, along with prior ICU LOS, mechanical ventilation status, vasopressor use, and definitive antibiotic choice, are important predictors of survival in this population.

1. Introduction

Development of multidrug-resistant (MDR) Gram-negative infection is associated with an increased risk of both all-cause and attributable mortality compared to non-MDR Gram-negative infection [1-3]. The Infectious Diseases Society of America has identified Enterobacteriaceae, *Pseudomonas aeruginosa*, and *Acinetobacter baumannii* as emerging organisms of concern for multidrug resistance, and have encouraged research in this area [4]. In addition to increasing risk of mortality, these MDR Gram-negative infections also increase other complications and cost [5-7].

Several studies have evaluated risk factors for mortality in patients with MDR Gram-negative infections. A meta-analysis of patients with MDR Gram-negative infections found that mechanical ventilation, ICU stay, septic shock, delay in definitive treatment, higher APACHE II score, underlying disease, and increasing age were associated with increased risk of mortality [1]. While a number of studies have demonstrated that critical illness is associated with increased mortality among patients with MDR Gram-negative infections, additional data on mortality specific to ICU patients, particularly critically ill surgical patients, with these infections is limited and sometimes conflicting [1,8,9]. The lack of sufficient data related to mortality in this population impedes clear clinical discussions and decision-making for these critically ill patients.

A better understanding of the characteristics and outcomes of patients with MDR Gram-negative infections is needed, specifically for critically ill surgical patients. The objective of this study was to determine the prevalence of in-hospital mortality among critically ill surgical patients with resistant Gram-negative infections and to identify factors associated with in-hospital mortality in this population.

2. Materials and methods

2.1. Study population

This case-control study was conducted at The Johns Hopkins Hospital in Baltimore, MD. Patients who were admitted to one of two surgical

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intensive care units (SICUs) between January 2011 and December 2014 and had a carbapenem-resistant Enterobacteriaceae (CRE), multidrug-resistant (MDR) *Pseudomonas aeruginosa*, or MDR *Acinetobacter* spp. infection were included in the study. All culture sources were included to determine the presence of the bacteria of interest. An expert review panel consisting of two clinical pharmacy specialists in surgical critical care and one infectious disease physician, all of whom were study authors, determined the presence of active infection versus colonization through review of antibiotic therapy and duration, progress notes, and relevant clinical data in the electronic medical record (EMR). Only patients determined to have active infection were included in the study. Demographics, comorbidities, surgical procedures, and antibiotic therapy data for the duration of hospitalization were collected from the EMR, and these factors were evaluated for association with in-hospital mortality. The study was approved by the Johns Hopkins Medicine Institutional Review Board.

2.2. Definitions

The first culture obtained from patient during a SICU admission that grew CRE, MDR *Pseudomonas aeruginosa*, or MDR *Acinetobacter* spp. was defined as the index culture. This culture was used to determine study inclusion. The MDR organisms that grew on the index culture were defined as the index organisms.

Susceptibility results for the index organisms were reported in the EMR. Enterobacteriaceae were defined as CRE if they were 1) resistant to a carbapenem or 2) non-susceptible (i.e. intermediate or resistant) to a carbapenem and resistant to ceftriaxone. The CRE definition used in this study was developed to combine the two definitions of CRE from the Centers for Disease Control and Prevention (CDC) that existed during the study period [10]. *P. aeruginosa* were defined as MDR if they were resistant to all tested antimicrobial agents in at least three of the following classes: 1) antipseudomonal penicillins and cephalosporins, 2) carbapenems, 3) fluoroquinolones, and 4) aminoglycosides. *Acinetobacter* spp. were defined as MDR if they were resistant to all tested antimicrobial agents in at least three of the following classes: 1) ampicillin/sulbactam, 2) antipseudomonal cephalosporins, 3) antipseudomonal carbapenems, 4) fluoroquinolones, and 5) aminoglycosides. These definitions are similar to those proposed by a joint initiative by the CDC and the European Center for Disease Prevention and Control (ECDC) [11].

Empiric antibiotic therapy was defined as the antibiotic therapy that the patient was receiving by the end of post-index culture day 1. Inadequate empiric antibiotic therapy (IEAT) was defined as empiric therapy that did not include an agent to which the index organism was susceptible. Definitive therapy was defined as antibiotics that the patient received after the index culture results were available.

Achievement of source control was determined from documentation in progress notes in the EMR. Source control was defined as achieved if a progress note documented the achievement of source control, and as not achieved if a progress note did not document the achievement of source control. Source control was defined as not applicable if the index culture source was urinary or respiratory.

The expert review panel assessed adequacy of empiric and definitive therapy, and achievement of source control according to documentation in the EMR.

2.3. Statistical analysis

Bivariate comparisons were made using the χ^2, Fisher's exact test, Student's *t*-test, and Mann-Whitney *U* test, as appropriate. A *p*-value <0.05 was considered statistically significant for all tests. A multivariate logistic regression model was also used to identify factors predictive of in-hospital mortality. Variables with a *p*-value <0.2 in univariate analysis were considered for inclusion in the model. All statistical tests were performed using Stata version 13 (StataCorp, College Station, TX, USA).

3. Results

3.1. Patient characteristics and culture results

A total of 62 patients met inclusion criteria. There were no significant differences in demographics or baseline comorbidities between survivors and non-survivors (Table 1). As compared to survivors, more non-survivors were mechanically ventilated and had vasopressor use prior to index culture (Table 1). All non-survivors were mechanically ventilated prior to index culture compared to 63.4% of survivors ($p = 0.001$). ICU and hospital length of stay prior to index culture were greater in non-survivors than in survivors (Table 1).

Index culture information is shown in Table 2. CRE were the most common index organisms, followed by MDR *Pseudomonas aeruginosa* and MDR *Acinetobacter* spp., respectively. An index culture that grew CRE was present in 80.7% of patients in the study (Table 2). Additional information about the specific CRE index organisms is also shown in Table 2. Index culture characteristics were similar between survivors and non-survivors.

3.2. Antibiotic therapy and source control

Data regarding antibiotic therapy and other interventions are shown in Table 3. Most patients received piperacillin/tazobactam during their hospitalization prior to index culture. Prior antibiotic exposure was similar between survivors and non-survivors (Table 3).

There was wide variety in empiric antibiotic therapy for Gram-negative organisms, but piperacillin/tazobactam monotherapy was the most common empiric regimen (Table 3). IEAT was present in 72.6% of patients. More patients in the survivor group had IEAT as compared to non-survivors (80.5% vs. 57.1%, $p = 0.05$). One patient received no empiric therapy, as there was presumably low suspicion for active infection at the time of index culture.

Definitive therapy for Gram-negative organisms was also variable, with carbapenem monotherapy being the most common choice (Table 3). Comparing survivors and non-survivors, definitive therapy was largely similar. Use of other definitive combination therapy (i.e. a combination other than an aminoglycoside plus colistin or a carbapenem plus aminoglycoside or colistin; see Table 3 footnotes for additional information) was more common among non-survivors vs. survivors (42.9% vs. 17.1%, $p = 0.03$).

Source control status was notably different between survivors and non-survivors, with achievement of source control being more common in survivors (Table 3). Scenarios in which source control was not applicable (pneumonia and urinary tract infection) were similarly distributed between survivors and non-survivors.

A subgroup analysis of antibiotic therapy among patients with CRE is shown in Table 4. Prior antibiotic exposure, empiric antibiotic selection, definitive antibiotic selection, and IEAT occurrence were similar in this subgroup analysis as compared to the entire study population (Tables 3 and 4). No significant differences were noted between survivors and non-survivors with CRE (Table 4).

3.3. In-hospital mortality

Twenty-one patients (33.9%) experienced in-hospital mortality. Variables included in the multivariate logistic regression assessing in-hospital mortality are shown in Table 5. Achievement of source control and other definitive antibiotic therapy were the only factors shown to be independently associated with in-hospital mortality (Table 5). Achievement of source control was associated with a decrease in mortality, while use of other definitive antibiotic therapy was associated with an increase in mortality. Of note, all patients in the non-survivor group received mechanical ventilation prior to index culture (Table 1), prohibiting this variable from being included in the regression model due to collinearity.

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