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Prior use of four invasive procedures increases the risk of *Acinetobacter baumannii* nosocomial bacteremia among patients in intensive care units: a systematic review and meta-analysis

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Background: *Acinetobacter baumannii* is considered a leading cause of nosocomial bloodstream infections in intensive care units (ICUs), but there is disagreement as to whether certain invasive ICU procedures increase the risk of this infection. To help address this question, we performed a systematic review of the literature on whether previous catheterization (central venous, arterial, and urinary), mechanical ventilation, nasogastric tube use, and abdominal or thoracic drainage are associated with the development of *A. baumannii* nosocomial bacteremia in ICUs.

Methods: Two reviewers searched PubMed, EMBASE, and Medline for the period January 1999 to February 2013. For each of seven invasive procedures, patients in the included studies were classified into two groups: those who had previously undergone that procedure and those who had not. The frequencies of *A. baumannii* nosocomial bacteremia were determined for each group.

Results: Five studies were included in the meta-analysis: three provided data for thoracic drainage, four for abdominal drainage, and five for the other invasive procedures. The following prior interventions were associated with an elevated risk of *A. baumannii* nosocomial bacteremia: mechanical ventilation (odds ratio (OR) 4.79, 95% confidence interval (CI) 3.09–7.43), central venous catheterization (OR 6.25, 95% CI 2.58–15.11), urinary catheterization (OR 2.55, 95% CI 1.49–4.36), and nasogastric tube use (OR 4.70, 95% CI 2.79–7.91).

Conclusions: Available evidence suggests that prior central venous or urinary catheterization, mechanical ventilation, and nasogastric tube use are associated with a higher risk of *A. baumannii* nosocomial bacteremia in the ICU.

1. Introduction

Acinetobacter baumannii, a non-fermenting Gram-negative aerobic coccobacillus, is emerging as an important nosocomial pathogen worldwide, especially in intensive care units (ICUs).[1,2] In recent years, it has been designated a 'red alert' human pathogen and has caused considerable concern in the medical community.[3] In fact, *A. baumannii* is considered a leading cause of nosocomial bloodstream infections in ICUs.[4–6] The clinical course of these bloodstream infections varies from benign transient bacteremia to fulminant septic shock, with a crude mortality rate as high as 52%.[2]

Studies comparing ICU patients with and without *A. baumannii* bloodstream infection have reported several risk factors for *A. baumannii* nosocomial bacteremia, including organ failure, large burn wound area, prior use of antibiotics, major surgical procedures, immunosuppression, and prior chemo- or radiotherapy.[7–12] While some studies have also suggested the prior use of invasive procedures to be a risk factor for *A. baumannii* nosocomial bacteremia, the strength of this association is questionable because studies have differed widely in design, sample size, and patient age, as well as in which invasive procedures they have analyzed and on whether they analyzed endemic colonization or epidemic outbreaks.[13] This highlights the need for more rigorous

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systematic review and analysis to determine the influence of specific invasive procedures on the risk of *A. baumannii* nosocomial bacteremia.

Therefore we performed a systematic review of the literature to examine the association between the risk of *A. baumannii* nosocomial bacteremia and seven invasive procedures: central venous, arterial, and urinary catheterization; mechanical ventilation; nasogastric tube use; and abdominal and thoracic drainage.

2. Methods

2.1. Search strategy

Both a specialist in infectious disease and a professional epidemiologist searched PubMed, EMBASE, and Medline databases using the following search terms to identify relevant studies published in the period January 1999 to February 2013: '*Acinetobacter baumannii*', 'bacteremia OR bloodstream infection', 'risk factors OR predictors'. Results were limited to 'All Adults' without any language restriction. Reference lists in the selected articles and relevant review articles were also searched to identify additional studies. When multiple relevant abstracts from scientific conferences were identified in the searches of the literature databases, separate searches of all abstracts from those conferences were conducted.

2.2. Study selection

Studies were selected if they (1) had a case–control or cohort design, whether prospective or retrospective, or a randomized controlled design; (2) diagnosed *A. baumannii* nosocomial bacteremia (or nosocomial bloodstream infection) according to the criteria of the Centers for Disease Control and Prevention;[14] and (3) examined whether one or more of seven prior invasive procedures (central venous, arterial or urinary catheterization; mechanical ventilation; nasogastric tube use; abdominal or thoracic drainage) was a risk factor or predictor for *A. baumannii* nosocomial bacteremia in adult ICU patients. Studies examining patients in general wards were excluded, as were case reports, reviews, and comments or letters to the editor.

2.3. Data extraction

Data in the text, tables, and figures of the included studies were extracted independently by two authors (ZY, HYZ) using a standardized protocol and definitions. Disagreements were resolved through discussion. For each of the seven invasive procedures, patients in each study were classified into two groups: those who had undergone that prior intervention and those who had not. For each intervention, the proportions of patients in each of the two groups who developed *A. baumannii* nosocomial bacteremia were recorded.

2.4. Quality assessment of included studies

We assessed the quality of the included studies using the Newcastle–Ottawa Scale (NOS) for case–control and cohort studies.[15] We developed an NOS-based scale for scoring the studies (score range, 0–9 points).

2.5. Statistical analysis

The meta-analysis was performed using RevMan 5.2.7 (Cochrane Collaboration). Pooled odds ratios (ORs) and 95% confidence intervals (CIs) were calculated for all outcomes. Statistical heterogeneity between studies was assessed using a Chi-square test in which $p < 0.10$ was taken as the threshold of significant heterogeneity, or by calculating I^2, with $I^2 \geq 50\%$ considered evidence of heterogeneity. The Mantel–Haenszel fixed- or random-effects method was used to perform a meta-analysis of outcomes depending on the assessed heterogeneity. Furthermore, subgroup meta-analyses were performed to address heterogeneity when a sufficient number of studies could be included.[16] Publication bias was explored graphically using funnel plots.[16]

3. Results

Of the 258 relevant articles identified in the databases, 232 were excluded based on title and abstract screening and 21 were excluded after reading the full text (Figure 1). The remaining five studies were included in the final meta-analysis, although not all studies underwent meta-analysis for all invasive procedures. Key characteristics of the included studies and the risk factors that they assessed are presented in Table 1.

The studies had various designs: prospective cohort (one), retrospective case–control (two), and retrospective, matched case–control (two). The studies were of reasonably high quality: their rating based on the NOS ranged from 7 to 9 points, with an average score of 7 points (Table 2).

The five studies showed considerable overlap in the invasive procedures that they examined, allowing us to include most or all of them in meta-analyses of the various invasive procedures and risk of *A. baumannii* nosocomial bacteremia (Table 3). Five studies reported data on prior mechanical ventilation, and these data underwent meta-analysis using a fixed-effect model, since no statistically significant heterogeneity was found ($I^2 = 0\%$, $p = 0.48$). The pooled OR for *A. baumannii* nosocomial bacteremia in patients with prior mechanical ventilation relative to those without prior ventilation was 4.79 (95% CI 3.09–7.43, $p < 0.001$). All five studies also reported data on prior central venous catheterization, which showed no statistically significant heterogeneity ($I^2 = 0\%$, $p = 0.92$). Fixed-effect meta-analysis gave a pooled OR of 6.25 (95% CI 2.58–15.11, $p < 0.001$). Fixed-effect meta-analysis of data from all five studies on prior urinary catheterization ($I^2 = 17\%$, $P = 0.31$) gave a pooled OR of 2.55 (95% CI 1.49–4.36, $p < 0.001$). The same approach was used to perform a meta-analysis of the nasogastric tube data from the five studies ($I^2 = 23\%$, $p = 0.27$), giving a pooled OR of 4.70 (95% CI 2.79–7.91, $p < 0.001$). While all five studies also reported data on prior arterial catheterization, they showed significant heterogeneity ($I^2 = 67\%$, $p = 0.02$), so random-effects meta-analysis was used to generate a pooled OR of 1.35 (95% CI 0.62–2.93, $p = 0.44$).

Given the heterogeneity among the studies examining prior arterial catheterization, we performed subgroup analyses for that procedure based on whether the study involved 100–400 patients or numbers smaller or larger than this range, and on whether the study involved patients admitted to the burn ICU or to non-burn ICUs (Figure 2). Heterogeneity within each subgroup was lower than in the original set of studies, especially among studies analyzing 100–400 patients. The results were similar to those obtained without study stratification, suggesting that our results are robust.

The five studies did not all report data on thoracic and abdominal drainage. Data from three studies on thoracic drainage showed significant heterogeneity ($I^2 = 58\%$, $p = 0.09$), and so underwent meta-analysis using a random-effects model to obtain a pooled OR of 1.81 (95% CI 0.88–3.70, $p = 0.10$). Four studies reported data on prior abdominal drainage that did not show significant heterogeneity ($I^2 = 10\%$, $p = 0.34$). Fixed-effect meta-analysis gave a pooled OR of 1.13 (95% CI 0.71–1.78, $p = 0.61$).

In order to detect evidence of significant publication bias, we generated funnel plots of the meta-analysis for each of the seven