The impact of multidrug resistance in healthcare-associated and nosocomial Gram-negative bacteraemia on mortality and length of stay: cohort study

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Abstract

Multidrug-resistant Gram-negative bacteria (MDR-GNB) are an emerging public health threat. Accurate estimates of their clinical impact are vital for justifying interventions directed towards preventing or managing infections caused by these pathogens. A retrospective observational cohort study was conducted between 1 January 2007 and 31 July 2009, involving subjects with healthcare-associated and nosocomial Gram-negative bacteraemia at two large Singaporean hospitals. Outcomes studied were mortality and length of stay post-onset of bacteraemia in survivors (LOS). There were 675 subjects (301 with MDR-GNB) matching study inclusion criteria. On multivariate analysis, multidrug resistance was not associated with 30-day mortality, but it was independently associated with longer LOS in survivors (coefficient, 0.34; 95% CI, 0.21–0.48; $p < 0.001$). The excess LOS attributable to multidrug resistance after adjustment for confounders was 6.1 days. Other independent risk factors for higher mortality included male gender, higher APACHE II score, higher Charlson comorbidity index, intensive care unit stay and presence of concomitant pneumonia. Concomitant urinary tract infection and admission to a surgical discipline were associated with lower risk of mortality. Appropriate empirical antibiotic therapy was neither associated with 30-day mortality nor LOS, although the study was not powered to assess this covariate adequately. Our study adds to existing evidence that multidrug resistance *per se* is not associated with higher mortality when effective antibiotics are used for definitive therapy. However, its association with longer hospitalization justifies the use of control efforts.

Keywords: Antimicrobial drug resistance, cohort study, Gram-negative bacteraemia, length of stay, mortality
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Introduction

Antibiotic-resistant Gram-negative bacteria are a major public health threat, increasing in prevalence globally in both community and institutional settings [1]. The Antimicrobial Availability Task Force formed by the Infectious Diseases Society of America (IDSA) had identified three Gram-negative pathogens of particular importance, namely, extended-spectrum β-lactamase (ESBL)-producing Enterobacteriaceae, *Acinetobacter baumannii* and *Pseudomonas aeruginosa* [1]. These organisms are also major pathogens in Singaporean hospitals, where the prevalence of antibiotic resistance is high [2].

The perceived hazards of Gram-negative antimicrobial resistance stem from two interlinked concerns: diminishing therapeutic options for the treatment of infections caused by these bacteria [1], and the potentially greater negative impact on both clinical outcomes and healthcare costs [3–7]. Although the majority of published studies demonstrate an independent association between Gram-negative resistance and worse clinical outcomes [4–9], these results are not universal and may be confounded by the impact of delayed appropriate antimicrobial therapy, differing study designs and definitions of resistance, and potential biases in the selection of study subjects [3,10,11].

Nonetheless, accurate estimates of the impact of Gram-negative antimicrobial resistance are crucial for justifying interventions aimed at preventing or managing these infections, and for evaluating their effectiveness [12]. The primary objective of our study was to evaluate clinical outcomes associated with healthcare-associated Gram-negative bacteraemia, and to assess the independent effect of multidrug resistance on these outcomes.

Patients and Methods

Study design and setting

We conducted a dual-centre retrospective, observational cohort study at the two largest public sector hospitals in Singapore—the 1600-bed Singapore General Hospital and the 1400-bed Tan Tock Seng Hospital. The recruitment period was between 1 January 2007 and 31 July 2009, while the follow-up period was up to the point of discharge/death of the final subject.

Participants

Subjects were consecutive inpatients with healthcare-associated Gram-negative bacteraemia and sepsis due to Enterobacteriaceae, *Pseudomonas aeruginosa* and/or *Acinetobacter baumannii*. Only the first episode of bacteraemia was recorded for each subject. Subjects were identified from each hospital's microbiology laboratory database, and screened for eligibility by conformation with sepsis criteria at the time of bacteraemia by trained researchers [13]. Subjects with mixed Gram-positive and Gram-negative bacteraemia were excluded from the study.

We considered bacteraemia to be healthcare-associated if it fulfilled previously published criteria for nosocomial or healthcare-associated bacteraemia [14].

Data sources and variables

Demographical, clinical and microbiological variables as well as outcomes were collected from inpatient clinical, administrative and laboratory records.

Multidrug resistance was defined as resistance to all antimicrobial agents tested in three or more antibiotic classes [15]. This definition would encompass the majority of definitions of multidrug resistance in the published literature [16,17]. Antibiotic susceptibility testing—including screening for extended-spectrum beta-lactamase (ESBL) production—was performed using the Kirby–Bauer disk-diffusion method following Clinical Laboratory Standards Institute (CLSI) guidelines [18]. The antibiotic classes and antibiotics tested included β-lactam/β-lactamase inhibitors (amoxicillin/clavulanate, piperacillin/tazobactam and ampicillin/sulbactam), cephalosporins (ceftazidime and cefepime), fluoroquinolones (ciprofloxacin), aminoglycosides (gentamicin and amikacin), carbapenems (imipenem and meropenem), and polymyxins. Subjects with mixed multidrug-resistant (MDR) and non-MDR Gram-negative bacteraemia were classified as having MDR bacteraemia.

Severity of illness was scored using the Acute Physiology and Chronic Health Evaluation, version II (APACHE II), with variables taken at the day of positive cultures [19], while the Charlson [20] co-morbidity index was used as an aggregate measure for prognosticating subjects' co-morbidities. Intensive care unit (ICU) stay prior to bacteraemia was also recorded as a potential indicator of severity of illness. Other concomitant sites of infection were classified according to the National Healthcare Safety Network definitions [21].

We considered antibiotic therapy to be 'appropriate' if prescribed antibiotics had *in vitro* activity against all isolated organisms and appropriate doses were prescribed based on the Sanford Guide to Antimicrobial Therapy [22]. 'Empirical antibiotic therapy' was defined as antibiotics received within the first 24 h following blood cultures [23], whereas 'definitive antibiotic therapy' was defined as antibiotics received after 48 h post-blood cultures (i.e. when the organism had been identified and susceptibility profiles were available). For subjects who died within 72 h of blood cultures, definitive antibiotic therapy was not used as a variable for determining association with all outcomes.

The primary outcome was 30-day mortality, while the secondary outcome was length of hospitalization post-onset of bacteraemia (LOS) in survivors.

Bias and quantitative variables

Selection bias was minimized by inclusion of all subjects matching inclusion criteria during the study period. The distributions of quantitative variables were assessed and non-parametric analyses were selected for skewed distributions. For regression models, the data were transformed to the natural logarithmic scale to ensure normality.

Study size

For determination of the cohort size, we used the results of Schwaber and Carmeli's meta-analysis (pooled crude relative risk of 1.85 with regards to mortality and pooled crude mortality of 20% among non-ESBL patients) as the best compromise in view of the heterogeneity of existing studies [24]. We estimated that at least 267 hospital admissions with MDR bacteraemia, with a similar number of non-MDR bacteraemia, would be required to detect similar differences in mortality with a statistical power of 80% and a 5% significance level.