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Increased risk of death with recurrent *Pseudomonas aeruginosa* bacteremia☆

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ABSTRACT

This study aimed to characterize recurrent *Pseudomonas aeruginosa* blood stream infection (BSI). Positive blood cultures for *P. aeruginosa* were identified over a 3-year period from seven tertiary care hospitals. Patients with recurrent BSI were identified. Extensive epidemiological, clinical and outcome data were obtained. BSI recurrence was found to be uncommon with 9% of patients having a first relapse of BSI. Fourteen percent of these patients went on to have a second relapse of BSI. Significant variables associated with recurrence were the presence of a hematological malignancy or receiving recent corticosteroid therapy. Exposure to anti-pseudomonal beta-lactam therapy in the 30 days prior to the BSI was more likely in the patient with the recurrent BSI episode. Recurrence was associated with increased mortality when compared to the primary BSI episode. Knowledge of a patient's prior antibiotic therapy may be useful in ensuring effective empirical therapy in the recurrent BSI episode.

1. Introduction

The Centers for Disease Control and Prevention found that *P. aeruginosa* accounted for 7.1% of health care acquired infections (HCAI) in the United States in 2011. It was the third most common gram negative cause of blood stream infections (BSI) (Magill et al., 2014). This is an infection with considerable mortality with rates of up to 42% being described depending on the population studied (Johnson et al., 2009). Although primary infection has been well studied, cohort studies looking at *P. aeruginosa* BSI over the last decade have typically excluded recurrent infection episodes. Recurrent *P. aeruginosa* infection has been described in the literature in 3 patient groups: liver transplantation, human immunodeficiency virus infection (HIV) and bone marrow or stem cell transplantation patients (Hakki et al., 2007; Korvick et al., 1991; Mendelson et al., 1994). In clinical practice recurrent infection is also seen outside these patient groups. This tertiary multicentre study aimed to: a. further characterize the patient in whom a recurrent *P. aeruginosa* BSI occurs; b. look at time to infection recurrence; and c. to characterize the variables that may place an individual at risk for recurrence of this infection.

2. Materials and methods

2.1. Study design

The study was conducted at 7 tertiary care hospitals in Brisbane, Australia. The hospitals range in size from 207 to 929 beds. Together they provide a specialized and broad medical, surgical and intensive care for an urban population of 2.24 million. Positive blood cultures for *P. aeruginosa* were identified over the 3-year time period of January 1, 2008, to December 31, 2010, from the laboratories servicing the hospitals. A BSI episode was identified as the 14 day time period from the date of the first positive blood culture. Patients were excluded if they met any of the following criteria: age less than 18 years, the patient was not admitted to hospital post blood culture collection, the sentinel blood culture was not taken at a participating hospital, there was no antibiotic treatment of the blood culture isolate, the patient was transferred to another institution within 72 hours of the primary blood culture being collected, the patient's case notes could not be obtained or the patient died within 7 days of the primary BSI episode. Polymicrobial BSI's or BSI episodes in which another significant pathogen was grown from a blood culture 10 days prior to 14 days post the sentinel blood culture collection with *P. aeruginosa* were not excluded.

The BSI episodes studied were divided into four groups: a. primary BSI episodes from patients who survived 7 days after the initial BSI and did not go on to have a recurrent BSI within the 3-year study period; b. the primary BSI episode in a patient who survived 7 days after the initial BSI and that went on to have recurrent infection in the 3 year study period; c. the primary relapse episode of BSI in the patient with recurrent infection; and d. any further relapsing BSI episodes in the patient

☆ Conflicts of interest: None

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that went on to have a further BSI episodes provided they survived 7 days post the preceding BSI episode. The latter group was utilized for descriptive purposes only. Ethics approval to carry out the study from all participating hospitals and laboratories was obtained.

2.2. Data collection and definitions

2.2.1. Assessed clinical variables

The following data were collected from all patient case notes in a retrospective fashion: age, sex, origin of infection (hospital, health-care or community acquired), patient location at the time of the sentinel blood culture collection, co-morbidities, Charlson's weighted comorbidity index (CCI), invasive medical devices in the 7 days prior to the episode, surgery in the 14 days prior to the episode, immunosuppressive therapy or blood products in the 30 days prior to the episode, source of the bacteraemia, antimicrobial therapy started from 30 days prior to post primary bacteremia and the Pitt bacteraemia score (Charlson et al., 1987; Chow and Yu, 1999). From the laboratory, details of any other blood culture isolates from 10 days prior to 30 days post the episode were obtained. In addition antibiograms of the *P. aeruginosa* isolates of interest, other sites of growth of *P. aeruginosa* within 48 hours before or after positive blood cultures for *P. aeruginosa* were recorded, as were periods of neutropenia.

2.2.2. Definitions

A *bacteremic episode* is defined as the 14 day time period from the date of the first positive blood culture for *P. aeruginosa*. *Recurrent infection* was defined as subsequent culture of *P. aeruginosa* outside the primary BSI episode. A *hospital acquired infection* (HAI) is defined as a positive blood culture obtained from a patient after 48 hours of hospitalization or within 48 hours of discharge. A *healthcare associated infection* (HCAI) is defined as a positive culture obtained from a patient at the time of hospital admission or within 48 hours of admission if the BSI fulfilled any of the following criteria: 1. Is a complication of an indwelling medical device; 2. Occurs within 30 days of a surgical procedure where the BSI is related to a surgical site infection; 3. An invasive instrumentation or incision related to a BSI was performed within 48 hours before the onset of infection. If the timing of onset was longer than 48 hours there must be compelling evidence that the infection was related to an invasive device or procedure; 4. Received therapy with temporary intravenous access in the 48 hours before the onset of infection. If the timing of onset was longer than 48 hours there must be compelling evidence that the infection was related to the invasive device or procedure; 5. Associated with neutropenia ($< 0.5 * 10^9$/L) contributed to by cytotoxic therapy; or 6. The patient resided in a nursing home. A *community acquired infection* (CAI) is defined as a positive culture obtained at the time of hospital admission or within the first 48 hours after admission which does not fit the criteria for a HCAI (www.safetyandquality.gov.au/wp-content/uploads/.../bsidefinejun05.pdf, n.d.). *Underlying disease* refers to all conditions present at admission and diagnosed with up to 48 hours of the BSI. The definition of *source of infection* were defined as per modified from Centers for Disease Control and Prevention definitions (Horan et al., 2008) and line related infections were as per modified Australian Infection Control Association guidelines (www.safetyandquality.gov.au/wp-content/uploads/.../bsidefinejun05.pdf, n.d.). A line associated bacteremia was also defined as a bacteremia in the presence of a central access line in the absence of another source of infection. *Polymicrobial infection* referred to the growth of another significant bacterial isolate from the sentinel blood culture collection in which *P. aeruginosa* was also identified. *Adequate empirical therapy* referred to those patients who received an active agent against *P. aeruginosa* that was considered appropriate based on analysis of the antibiogram of the isolate causing the infection in each episode. Beta-lactam/beta-lactamase inhibitor therapy excluding amoxicillin-clavulanate, carbapenem therapy excluding ertapenem, ceftazidime, cefepime and ciprofloxacin (intravenous) were considered potentially appropriate antipseudomonal agents. This therapy needed to start within 24 hours of the blood culture being drawn; the antibiotic had to have been administered for at least 48 hours, with the single exception of patients who died before 48 hours, who were included if death occurred after 1 complete day of therapy with the assigned regimen. *Adequate targeted therapy* referred to patients who received an active agent against *P. aeruginosa* based on the susceptibility profile of the isolate. Targeted therapy had to have started within 5 days of the blood culture being drawn and to be administered for at least 5 days. For patients who died while on targeted therapy they needed to have completed at least 1 complete day of therapy with the targeted regimen. Patients with the above criteria who continued with the same therapy that had been administered empirically once susceptibility results became available were also included. The utilization of oral therapy was also examined by the identification of patients who made a rapid change to oral therapy (RCOT) or made a late change to oral therapy (LCOT). The RCOT cohort included any patient who received targeted therapy with the above criteria but the targeted therapy included a change to oral ciprofloxacin within the first 5 days of targeted therapy. The *LCOT* cohort included any patient who after a minimum of 5 days of targeted intravenous therapy had received at least 2 days of oral ciprofloxacin in the second 5 day phase of potential antibiotic therapy. If the patient had been rapidly changed to oral ciprofloxacin as per the RCOT cohort they were excluded from this group. Only mono-microbial BSI episodes were studied regarding the adequacy of antibiotic therapy.

2.3. Microbiological methods

During the study period the blood cultures were processed by the BACTEC system (Becton Dickinson Microbiology Systems) with an incubation period of 5 days. Isolates were identified by the VITEK 2 system (bioMerieux, Balmes-les-Grottes, France). Antimicrobial susceptibility testing was performed by a microdilution method on the VITEK 2 system. Clinical and Laboratory Standards Institute (CLSI) breakpoints were used to define susceptibility or resistance to the antimicrobial agents tested.

2.4. Statistical analysis

The relationship between categorical variables was compared using the chi-square test or Fishers exact test. The student's t test was used for continuous variables. To identify independent risk factors for recurrent infection, variables with a p value of <0.2 on the univariate analysis were included in a backward stepwise multivariate logistic regression model. The variable was also required to make clinical sense to be included in the model. Variables with greater than 10% of missing data were excluded from the multivariate analysis to allow inclusion of the maximal number of patient episodes in analysis of associations with recurrent infection. To also prevent over fitting of data variables with less than 10% of the cohort having the presence of that factor were also excluded. The fit of the model was assessed by the standardized Pearson test. The analysis was done using Stata software (version 13; StataCorp LP).

3. Results

This study retrospectively reviewed 595 episodes of *P. aeruginosa* BSI from 541 patients in 7 tertiary care hospitals in the city of Brisbane, a capital city of Australia, over a 3 year period. BSI episodes were excluded according to pre-defined study criteria (Fig. 1). This left 487 BSI episodes for analysis representing 441 patients. Over the 3 years of the study, of those patients that survived to at least 7 days post the primary infection, 41 of 441 (9%) patients went on to have a primary relapse episode of *P. aeruginosa* BSI. Of the 35 patients that survived to 7 days post the first BSI relapse episode, a further 5 patients (14%) went on to have a second relapse episode of BSI. Only 2 patients went on to have a third BSI relapse and 1 patient a fourth BSI relapse. The median time to the