Risk factors for mortality in Acinetobacter calcoaceticus–baumannii bacteraemia

Asmita A. Mehta1, V. Anil Kumar2, Kumari Indira K1, Suresh G. Nair3, Kavitha R. Dinesh2, Sanjeev K. Singh4

1Department of Pulmonary Medicine, Amrita Institute of Medical Sciences, Ponekara, Kochi–682041, Kerala, India
2Department of Microbiology, Amrita Institute of Medical Sciences, Ponekara, Kochi–682041, Kerala, India
3Departments of Anaesthesia and Critical Care, Amrita Institute of Medical Sciences, Kochi, Kerala, India
4Department of Medical Administration, Amrita Institute of Medical Sciences, Kochi, Kerala, India

ARTICLE INFO

Article history:
Received 11 June 2012
Received in revised form 6 June 2012
Accepted 16 November 2012
Available online 28 December 2012

Keywords:
Acinetobacter calcoaceticus–baumannii
Blood culture
Mechanical ventilation
Colonization
Diabetes mellitus
End stage renal disease

ABSTRACT

Objective: To determine the risk factors associated with mortality in Acinetobacter calcoaceticus–baumannii (Acb) complex blood stream infection. Methods: This was an observational study conducted in tertiary care hospital of South India. All patients with blood culture positive for Acb complex from January 2008 to December 2009 were included and a standardized abstraction form was used to abstract data. $P$ value was calculated by Chi square test. Univariate analysis was done by using 2x2 tables and the variables with $P$ value of $<0.1$ were further subjected to multivariate analysis. Multivariate analysis was done by logistic regression method. Results: After excluding the polymicrobial infections and duplicate isolates from the same patients, 81 cases were included in our study. Out of 81 patients, 20 (24.6%) patients had positive isolate from body secret other than blood for Acb complex, majority were hospitalized in intensive care unit (74%), had indwelling vascular catheters (68%) and were mechanically ventilated (61%). Multi drug resistant phenotypes were seen in 56 (69.1%) isolates and among them 13 (16%) were resistant to carbapenems. Univariate analysis showed renal disease, diabetes mellitus, use of mechanical ventilation and absence of appropriate antibiotic therapy, leucopenia, thrombocytopenia and raised prothrombin time were related to increased mortality in Acb complex bacteraemia. However, in multivariate analysis independent risk factors for mortality in Acb complex bacteraemia were platelets of less than 1.5ap-related to increased mortality in Acb complex bacteraemia. However, in multivariate analysis independent risk factors for mortality in Acb complex bacteraemia were platelets of less than 1.5

Conclusions: Thrombocytopenia and absence of appropriate antibiotics were risk factors associated with mortality in Acb bacteraemia. Patients with blood culture showing Acb complex bacteraemia with above findings should be attended with aggressive management. Clinician of hospitals with high incidence of Acb complex bacteraemia, should predict the chances of such infection even prior to blood culture reports are available, and should initiate appropriate antibiotics according to their institution antibiogram.

1. Introduction

The impact of nosocomial blood stream infection on the outcome of critically ill patients has been extensively studied, with an attributable mortality rate ranging from 19% to 35%[1–4]. Members of the Acinetobacter calcoaceticus–baumannii complex (Acb complex) are the predominant Acinetobacter in clinical settings, and isolates are usually multi–resistant, complicating therapy and frequently causing outbreaks. Colonization by Acinetobacter spp, in healthy people and damaged tissue is common due to the preference for moist environment[5]. It is widely distributed in nature and in the hospital environment causing opportunistic infections in debilitated patients especially in intensive care units[5]. Acinetobacter spp, is included in the list of six top priority dangerous drug resistant microbes, released by Infectious Disease Society of America[6]. Clinical infections caused by Acb complex include pneumonia, meningitis, bacteraemia, soft–tissue infections, surgical site infections, peritonitis, endocarditis, and catheter–related and urinary tract infections[7]. Frequent developments of multiple antimicrobial resistances has enhanced the virulence of this pathogen severely restricting the therapeutic options available for infected patients, thereby increasing the length of stay in intensive care unit (ICU) and mortality[8,9]. As the incidence of Acinetobacter blood stream...
infection (BSI) is on the rise, our study aims to determine the risk factors associated with mortality in such cases.

2. Material and methods

We conducted an observational study to determine the risk factors associated with mortality of all patients who had a positive blood culture for Acb complex from January 2008 through December 2009 at a tertiary care teaching institute in South India. Data were abstracted using a standardized abstraction form.

2.1. Various definitions

2.1.1. A case of Acb complex sepsis

A case of Acb complex sepsis was defined as any patient with clinical symptoms of infection growing Acb complex in at least one blood culture bottle. Patients with polymicrobial infections were excluded and patients with only one isolate were included in the study.

2.1.2. Nosocomial bacteraemia

Nosocomial bacteraemia was defined on the basis of the isolation of Acb complex from blood cultures 48 h after admission with features of systemic inflammatory response syndrome (SIRS)[10,11].

2.1.3. Colonization

Colonization was defined as the presence of Acb complex in secretions or excretions, on mucous membrane, in open wounds or skin without any adverse clinical signs or symptoms. The following clinical characteristics were recorded: Sex, age, duration of hospital stay, need for mechanical ventilation, use of central venous catheter, presence of underlying disease(s), history of prior and appropriate antibiotic therapy, days of admission before index culture, fatal outcome (death) if observed.

2.1.4. Appropriate antibiotics treatment

Appropriate antibiotics treatment was considered if the patient received at least one antibiotic that was sensitive in vitro with /without other measures like removal of indwelling catheter, regular dressing of wound or surgical drainage.

2.1.5. Prior antimicrobial therapy

Prior antimicrobial therapy was defined as the use of a systemic antimicrobial agent for at least 72 h within the 2 weeks preceding the date of the positive-culture.

2.1.6. Appropriate empirical antibiotic therapy

Appropriate empirical antibiotic therapy was defined as the administration of appropriate therapy soon after index blood culture, e.g. within 24–48 h. The primary outcome measure was in-hospital mortality. Institute Ethical committee had approved the study as per international guidelines[12].

2.2. Clinical specimens, Acinetobacter identification and sensitivity testing

For culture 10 mL of blood was collected by aseptic procedures and inoculated into BACTEC™ Plus Aerobic/ F or BacT/Alert 3D bottles and was placed in the BACTEC 9240 or BacT/Alert 3D blood culture instrument with in 2 h of collection. Identification and susceptibility testing was done either manually using standard biochemical test or by automated ID 32GN Mini API system (BioMerieux, Inc., St. Louis, MO). Specific phenotypic characteristics include the appearance of cocci or coccobacilli on Gram stain, the ability to grow on MacConkey agar, and resistance to penicillin. Major genus characteristics include the inability to ferment glucose (non–fermenter), lack of oxidase production (oxidase negative), and non–motility. Antibiotic sensitivity was determined using the disc diffusion method, according to the Clinical and Laboratory Standards Institute guidelines[13]. The microorganism was defined as MDR if it was resistant to more than three of the following eight antimicrobial agents: ampicillin/sulbactam, aztreonam, ceftazidime, ciprofloxacin, gentamicin, imipenem, piperacillin and trimethoprim/sulfamethoxazole[14].

2.3. Statistical analysis

Distribution and frequencies of all important variables were done using descriptive statistics. All P values were based on 2–tailed tests. Reported P values are for the chi-square test unless stated otherwise. Univariate analysis was done to test association between prognostic variables and response variables. Variables with P value <0.1 were included in multivariate logistic regression using enter method. A P value of <0.05 was considered to be statistically significant. Kaplan–Meir methods were used for the survival analyses from the day of hospital admission. Statistical analysis was conducted using SPSS software (SPSS–11.0 version).

3. Results

3.1. Base line demographics

During the two year study period our clinical microbiology laboratory received 28 773 blood culture bottles of which 8.8% (2 552) were found to be positive. Among the 2 552 isolates 126 (4.9%) were Acb complex. After excluding the polymicrobial infections and duplicate isolates from the same patients 81 cases were included in our study. Patients’ characteristics are shown in (Table 1).

3.2. Duration of hospital stay prior to index culture
The mean duration of stay in hospital before index culture came positive for Acb complex was 10 days (range 0–67 days).

### 3.3 Monthly distribution of Acb bacteraemia

The monthly incidence did not show any particular pattern and cases were uniformly distributed throughout the year.

### 3.4 Simultaneous Acb isolation from body fluid/sputum

Of the 81 cases 68% grew Acb complex in only one blood culture bottle, 30% in two bottles and in only two cases three bottles (from two sets of blood culture) were positive. Acb complex was also seen in 22.2% cases from sputum or endotracheal aspirate. In one case, Acb complex was also seen in 22.2% cases from sputum or pleural fluid and the other simultaneously from bile (from liver transplant patient) as well as peritoneal fluid. Presence of central venous catheter was documented in 39 (41.8%) cases, but only four catheter tips were sent for culture and none of them grew Acb complex.

### 3.5 Antibiotic susceptibility

Antibiotic susceptibility testing of the 81 non–duplicate Acb complex isolates by Kirby–Bauer disk diffusion method showed that 74% (40/81) were multi–drug resistant (MDR). Co–resistance was least in carbapenems (n=13, 16%) followed by cefoperazone/sulbactam (n=23, 28%), piperacillin / tazobactam (n=27, 33%), ciprofloxacin (n=44, 54%), gentamicin (n=45, 56%), piperacillin (n=51, 63%), ceftazidime (n=53, 66%) and cefoperazone (n=63, 77%). All the isolates were susceptible to colistin.

### 3.6 Risk factors for mortality in Acb bacteraemia

The patients were often admitted to the ICU (74%), and...
mechanically ventilated (61%). Appropriate empirical antibiotics were administered in 42 (52%) cases of which 13 (31%) died. Of the 39 (48%) patients who were administered inappropriate empirical antibiotics 22 (56.4%) died. The patients who died in spite of receiving appropriate empirical antibiotic therapy were more likely >50 years of age (11/13), had suffered a cerebrovascular accident (7/13) and were diabetic (5/13). Table 2 shows the univariate analysis of different clinical characteristics and their association with Acb complex bacteraemia. Age >52 years (\(P=0.037\)), diabetes mellitus (DM) (\(P<0.001\)), end stage renal disease (ESRD) (\(P<0.001\)), inappropriate empirical antibiotic treatment (\(P=0.018\)) and mechanical ventilation (\(P=0.002\)) were found to be associated with poor outcome. Other variables like chronic obstructive pulmonary disease (COPD), cardiac disease, history of surgical procedures, carbapenem resistance did not show statistically significant association with mortality. Laboratory parameters like platelet counts, total counts, serum creatinine, blood urea, and prothrombin time and their association with mortality were checked with univariate analysis (Table 3) and it showed low platelets \(<1.5 \text{lacs/mm}^3\) (\(P=0.041\)) and inappropriate empirical antibiotic therapy (\(P=0.027\)) were found to have significant association with mortality (Table 4). Survival analysis was done using Kaplan–Meier methods, which showed increased mortality in patients with platelets less than 1.5 lacs/mm\(^3\) and who received inappropriate antibiotics (Figure 1 and 2). The mortality difference appears to occur early on (prior to day 14) as shown in curves which also support conclusion that inappropriate initial antibiotic therapy may be independently associated with mortality.

**Table 3.** Laboratory parameters of patients with Acb bacteraemia and their relationship with mortality (\(n=81\)).

<table>
<thead>
<tr>
<th>Laboratory investigation</th>
<th>No of patients with fatal outcome (total no)</th>
<th>(P) value (OR, 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total white blood cell</td>
<td>19(42)</td>
<td>0.530 (0.9, 0.4–2.24)</td>
</tr>
<tr>
<td>4000—11 000</td>
<td>17(39)</td>
<td></td>
</tr>
<tr>
<td>Neutrophil</td>
<td>17(33)</td>
<td>0.202 (1.3, 0.8–2.1)</td>
</tr>
<tr>
<td>&lt;70%</td>
<td>19(48)</td>
<td></td>
</tr>
<tr>
<td>Platelets</td>
<td>20(59)</td>
<td>0.002 (2.424, 1.2–4.9)</td>
</tr>
<tr>
<td>&gt;1.5 lakh</td>
<td>16(22)</td>
<td></td>
</tr>
<tr>
<td>&lt;1.5 lakh</td>
<td>20(59)</td>
<td>0.000 (4.7, 1.8–12.4)</td>
</tr>
<tr>
<td>Blood urea</td>
<td>24(37)</td>
<td></td>
</tr>
<tr>
<td>&lt;40 mg/dL</td>
<td>11(39)</td>
<td>0.001 (4.7, 1.8–26.4)</td>
</tr>
<tr>
<td>&gt;40 mg/dL</td>
<td>20(59)</td>
<td></td>
</tr>
<tr>
<td>S. creatinine</td>
<td>16(20)</td>
<td></td>
</tr>
<tr>
<td>&lt;1.4 units</td>
<td>20(59)</td>
<td>&lt;0.001 (7.8, 2.3–26.4)</td>
</tr>
<tr>
<td>&gt;1.4 units</td>
<td>16(20)</td>
<td></td>
</tr>
<tr>
<td>Prothrombin time</td>
<td>7(26)</td>
<td>0.01 (3.78, 1.31–10.8)</td>
</tr>
<tr>
<td>&lt;15 seconds</td>
<td>25(43)</td>
<td></td>
</tr>
</tbody>
</table>

**Table 4.** Multivariate analysis (Logistic regression method).

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR (95% confidence interval)</th>
<th>(P) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.308 (0.312–5.485)</td>
<td>0.154</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>2.445 (0.501–11.537)</td>
<td>0.548</td>
</tr>
<tr>
<td>End stage renal disease</td>
<td>1.890 (0.190–18.180)</td>
<td>0.583</td>
</tr>
<tr>
<td>Ventilator support</td>
<td>4.430 (0.894–21.944)</td>
<td>0.051</td>
</tr>
<tr>
<td>Appropriate antibiotics given</td>
<td>0.2120 (0.056–0.807)</td>
<td>0.027</td>
</tr>
<tr>
<td>Platelet count&lt; 1.5 lac</td>
<td>3.773 (0.859–16.572)</td>
<td>0.044</td>
</tr>
<tr>
<td>S.creatinine&gt;1.5</td>
<td>1.717 (0.205–14.367)</td>
<td>0.733</td>
</tr>
<tr>
<td>Prothrombin time&gt; 15 seconds</td>
<td>2.288 (0.535–9.617)</td>
<td>0.567</td>
</tr>
<tr>
<td>Blood urea &gt;40 mg/dL</td>
<td>2.349 (0.538–10.257)</td>
<td>0.737</td>
</tr>
<tr>
<td>Carbapenem resistant</td>
<td>1.301 (0.201–8.433)</td>
<td>0.982</td>
</tr>
</tbody>
</table>

**4. Discussion**

Nosocomial bacteraemia caused by *Acinetobacter* species is
of great concern in critically ill patients, and the risk factors for this infection related mortality are not well established. This was an observational study to determine risk factors for mortality associated with Acinetobacter species bacteremia. Univariate analysis showed renal disease, diabetes mellitus, use of mechanical ventilation and absence of appropriate antibiotic therapy were associated with increased mortality. Patients with DM and ESRD frequently visit hospitals for treatment of complications like diabetic foot and dialysis respectively. Therefore these patients in addition to being immunocompromised have all the risk factors for Acb complex acquisition like prior use of multiple classes of antibiotics, invasive surgical procedures and frequent admission to the hospitals. The average duration of hospital stay was 14 days and was longer in case Carbapenem resistant Acb complex bacteremia. The average duration of hospital stay before positive index culture was 10 days. Similarly other studies have documented a hospital stay of more than one week with prior use of broad spectrum antibiotics as a significant risk factor for acquisition of Acb complex[5].

In present series, most of the patients were in ICU and were mechanically ventilated. These are the two common risk factors reported for Acinetobacter bacteremia in previous studies[16–18]. As documented previously, in our study also history of previous hospitalization and previous antimicrobial therapy were detected as important predisposing factors for Acinetobacter acquisition[19,20]. A recent history of surgical procedure was documented in 43% cases, consistent with previous studies which have shown an increase of Acinetobacter acquisition from various invasive procedures[14]. Risk of secondary bacteremia due to Acinetobacter increases many folds with tracheobronchitis and pneumonia[19–21]. We recorded 39% mortality in patients with carbapenem resistant Acb complex which were consistent with similar observations[22,23]. Appropriate empirical antimicrobial therapy significantly reduced the mortality attributed to Acb complex bacteremia which is similar to other reports[23,24]. Despite of appropriate antibiotics 31% of patients had fatal outcome this can be due to underlying disease or co-morbidity. In addition, we have to say that mortality is crude mortality and not attributable mortality due to ACB complex bacteremia.

Antibiotic susceptibility profile of Acinetobacter spp. differs in different countries and even among the wards of a given hospitals. With the prevalence of ESBL producing Enterobacteriaceae reaching epidemic proportions in many Indian medical centers, carbapenems are being extensively used creating an environment conducive for emergence of carbapenem resistant Acinetobacter isolates.[25]. The prevalence of MDR Acinetobacter in our study was 69% which was similar to previous study, [26] while carbapenem resistance was 16%. The most active agent against the carbapenem resistant isolates in our study was cefoperazone/ sulbactam with a susceptibility rate of 49%. Yun–Song Yu et.al studied 45 carbapenem isolates and found that cefoperazone/sulbactam and ampicillin/sulbactam were the only active agents, with a susceptibility of 63% and 43.5% respectively[15]. This may be due to the unique activity of sulbactam against Acinetobacter spp. sulbactam acts synergistically with cephalosporins in the treatment of infections caused by such isolates[27]. Last but not the least, efforts to remove invasive devices and equipment such as endotracheal tube or central venous catheter as soon as possible are needed to prevent development of MDR AB bacteremia among the colonized patients[28–30].

The antibiotics available for the carbapenem resistant Acb complex bacteremia are very few. Therefore, efforts should be taken to reduce incidence of Acb bacteremia, which starts with the primary measure like reducing intrinsic contamination and colonization of medical equipment or devices used for monitoring and therapy of patients, and hand hygiene to prevent cross infection in the ICU. Strength of the study was its adequately large sample size to say the results statistically significant. The study also addressed all the issues related to risk factors of mortality in Acb complex septicemia in extensive detail. In era of pan resistant micro organism, this study will help intensive care physician for identifying the risk factors for Acb complex septicemia as well as risk factors associated with increased mortality. Accurate data retrieval was possible, as our hospital is equipped with electronic medical record maintenance system.

Limitation is it was a retrospective single center study. Our hospital is a tertiary care hospital which has 213 ICU beds, which is a huge number. That might have affected the incidence of Acb complex bacteremia in present study and results may not be generalized.

The data may be helpful for planning the future multicentre study for more appropriate documentation of incidence and risk factors of Acb complex bacteremia. Due to financial constraints molecular based study on Acb for identifying the different strains was not conducted. To find out the virulent strain to start appropriate antibiotics may be future area of interest.

Present study showed that thrombocytopenia and absence of appropriate antibiotic therapy were associated with mortality. Early intervention and appropriate empirical antibiotics and setting with high prevalence of acinetobacter will helpful in preventing mortality.

Conflicts of interest statement

We declare that we have no conflict of interest.

References


