REVIEW

Nosocomial bacteremia due to *Acinetobacter baumannii*: epidemiology, clinical features and treatment

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Acinetobacter baumannii is an important cause of nosocomial infections in many hospitals. It is difficult to control and infection caused is difficult to treat due to its high resistance in the environment and its ability to develop resistance to antimicrobials. Bacteremia, followed by respiratory tract and surgical wound infections, is the most significant infection caused by *A. baumannii*. The known risk factors for *A. baumannii* bacteremia are invasive procedures and the use of broad-spectrum antimicrobials. Consequently, episodes of bacteremia due to *A. baumannii* occur most frequently in critically-ill patients admitted to an intensive care unit. The clinical manifestations of bacteremia by *A. baumannii* are not specific. The most common sources of bacteremia are intravascular catheters and the respiratory tract. *A. baumannii* bacteremia is associated with a high crude mortality rate, but it is difficult to distinguish morbidity and mortality attributable to *A. baumannii* from that attributable to the common and severe co-morbidity in these patients. *A. baumannii* is a bacterium that appears to have a propensity for developing multiple antimicrobial resistance extremely rapidly. These data are disturbing because the therapeutic possibilities decrease while inappropriate antimicrobial treatment contributes to patient mortality. Generally, imipenem is the most active agent against *A. baumannii*. However, the description of imipenem-resistant *A. baumannii* strains is becoming increasingly common. The usual treatment for *A. baumannii* bacteremia is an active β-lactam alone, preferably one with a limited spectrum. Before beginning treatment of a bacteremia by *A. baumannii*, it is very important to carry out a clinical evaluation of the patient to eliminate the possibility of a pseudobacteremia, and thereby avoid unnecessary treatment.

INTRODUCTION

In 1986 a new taxonomy was established for the *Acinetobacter* genus, of which *A. baumannii* is the most frequent species in clinical samples [1]. Since then *A. baumannii* has become a formidable pathogen and has been responsible for a number of nosocomial infection outbreaks. It is difficult both to control and infection caused is difficult to treat due to its high resistance in the environment and its ability to develop resistance to antimicrobials [2,3].

Bacteremia, followed by respiratory tract and surgical wound infections, is the most significant infection caused by *A. baumannii*. Its incidence varies considerably depending on periods of epidemic outbreak and the medical center itself [4–10]. Beck-Sagué et al. relate an incidence of 17 episodes per 1000 admissions during an epidemic outbreak [4]. However, Tilley et al. report an incidence of 0.3 episodes per 100 admissions when there is no epidemic [9]. In two large hospitals in Seville (Spain), the incidence of *A. baumannii* bacteremia has been variable, from 1.85 episodes per 1000 admissions in 1993 [7], to 0.6 episodes per 1000 admissions in 2000, and from 1.2 episodes per 1000 admissions between 1995 and 1997 [10] to 0.02 episodes in 1999.

Bacteremia due to *A. baumannii* is characteristically a nosocomial infection, particularly in intensive care units (ICUs). It is opportunistic and therefore almost exclusively affects predisposed patients who have undergone invasive procedures [5–7]. The known risk factors for *A. baumannii* colonization/infection are prolonged hospital stay, ICU stay, previous admission to another unit, enteral feeding and previous use of third-generation cephalosporins [11,12].

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EPIDEMIOLOGY AND RISK FACTORS

At the time of writing, *A. baumannii* is an important cause of nosocomial infections in many hospitals. Numerous outbreaks caused by a single clone have been reported, but the situation in most centers would be more appropriately described as endemic. In these hospitals, no more than 10–30% of patients from whom *A. baumannii* is isolated have bacteremia. Thus, the incidence of *A. baumannii* bacteremia in these hospitals should only be considered as the tip of the iceberg regarding the epidemiological situation of the organism.

Data from published studies showed some of the epidemiological features of *A. baumannii*. It is able to survive for long periods of time on inanimate surfaces in the patients' vicinity [13]. Environmental contamination is important as the organism can be transmitted from these surfaces to patients directly or through the hands of health-care workers. In addition, colonized and infected patients also represent an important reservoir of *A. baumannii* [14]. The organism may also be transmitted from patient to patient. In fact, the number of colonized patients has been described as the main risk factor for the acquisition of the organism by other patients admitted to the same unit or ward [15]. Health-care workers are usually only transiently colonized. Molecular analysis has demonstrated that the nosocomial infections caused by this organism within a hospital may be due both to epidemic and sporadic clones, and that the risk factors for the acquisition of epidemic or sporadic clones may be different [16].

Even though outbreaks caused by *A. baumannii* have been described in medical and surgical wards, ICUs are the most frequently affected areas. Colonization may be subsequently followed by an invasive infection [14]. In burn patients, previous colonization was strongly associated with the acquisition of bacteremia [17]. The potential risk factors for the development of bacteremia in other patients are invasive procedures (central venous catheterization, mechanical ventilation, surgery) and the use of broad spectrum antimicrobials. Consequently, episodes of bacteremia due to *A. baumannii* occur most frequently in critical patients admitted to an ICU [5,7], as these patients usually need more invasive procedures for longer periods of time, and frequently receive treatment with antimicrobials. In a multicenter study performed in the USA, patients with nosocomial bloodstream infections due to *Acinetobacter* spp., compared with patients with nosocomial bacteremia due to other Gram-negative pathogens, were more frequently in the ICU and were more frequently receiving mechanical ventilation [18]. Identified specific risk factors for *A. baumannii* bacteremia in ICU patients are immunosuppression, unscheduled admission, respiratory failure at ICU admission, previous antimicrobial therapy, previous sepsis and the high invasive-procedures index [19]. Neonatal ICUs may also be affected [20].

Microbiological typing has been performed in some studies dealing with bloodstream infections due to this organism. Beck-Sagué et al. described an outbreak of *A. baumannii* bacteremia in five ICUs associated with the use of contaminated pressure transducers [4]. Isolates cultured from pressure transducers and isolates cultured from the patients were identical in plasmid profiles. This technique was useful for presumptively identifying the source of the outbreak, which was controlled when the transducers were correctly sterilized. In another study, 87 episodes occurring in 79 patients in an 18-month period were reviewed [5]. Epidemiological molecular typing using pulsed-field gel electrophoresis revealed 11 different *A. baumannii* strains. The results of this study reflect a more complex situation, in which the episodes of bloodstream infections are caused both by epidemic and sporadic strains: 45, 21, eight and three episodes were caused by four epidemic strains, while the rest of the episodes were caused by sporadic strains. *A. baumannii* epidemic strains were also found in five hospitals in the multicenter study by Wisplinghoff et al. [18]. Interhospital spread of epidemic strains was not observed in that study.

A seasonal variation has been reported in nosocomial *Acinetobacter* infections, and in bacteremia in particular, with an increase in the incidence during the summer months [21]. Changes in temperature and humidity have been proposed as a possible explanation. The possible influence of decreased staff during summer months has not been studied.

CLINICAL MANIFESTATIONS

The clinical aspects of *A. baumannii* are not as well known as the epidemiological aspects and may

sometimes be confusing, as they are often grouped with other *Acinetobacter* species [5–9]. The clinical manifestations of bacteremia by *A. baumannii* are not specific. It may present as a transitory maculopapular rash affecting the palms of the hands and the soles of the feet in endocarditis patients [22], or as necrotic lesions of the skin and soft tissue [23]. Bacteremia by *A. baumannii* is often polymicrobial (19–35% of the cases) [5,7].

The most common sources of bacteremia by *A. baumannii* are intravascular and respiratory tract catheter [4,5,7]. An origin from surgical wounds, burns and the urinary tract is less common, and is very rare from endocarditis [5–8,22]. In up to 21–70% of the episodes, the origin of the bacteremia is unknown [6–8]. Some of these primary bacteremias could be secondary to undiagnosed vascular catheter infections or have an intestinal origin due to bacterial translocation. This is supported by the demonstration that digestive tract colonization by *A. baumannii* is more frequent and advanced in ICU patients [14,24].

The prognosis for bacteremia by *A. baumannii* is controversial. On one hand, its clinical relevance is under question, as the organism has few known virulence factors. On the other hand, clinical studies point out that bacteremia by *A. baumannii* results in septic shock in 25–30% of cases and that disseminated intravascular coagulation is also common [5,7].

ANTIMICROBIAL RESISTANCE

A. baumannii is a bacterium that appears to have a propensity for developing antimicrobial resistance extremely rapidly. Moreover, this resistance is multiple, causing serious therapeutic problems. Practices in ICUs contribute to the development of antimicrobial resistance in *A. baumannii* because the use of antimicrobials per patient and per surface area are significantly higher in this part of the hospital.

Susceptibility of *A. baumannii* to antimicrobials is considerably different among countries, among centres and even among the wards of a given hospital. These differences may reflect different patterns of antimicrobial usage and different epidemiological situations, including antimicrobial control measures and policies. The differences in resistance patterns among isolates emphasize the importance of local surveillance in determining the most adequate therapy for *A. baumannii* infections.

The known resistance mechanisms of *A. baumannii* to antimicrobials are: the production of broad-spectrum β-lactamases, aminoglycoside-modifying enzymes, changes in outer membrane porins and alterations in penicillin-binding proteins (PBP). Antimicrobial resistance has been tracked to plasmids, transposons and chromosomes [25].

Generally, imipenem is the most active agent against *A. baumannii*. In one study carried out in 49 US hospitals, in which 111 episodes of bacteremia by *A. baumannii* were analyzed, imipenem was active in vitro (CMI90 1 mg/L; 100% of the susceptible isolates) [17]. However, the description of imipenem-resistant *A. baumannii* strains is increasingly more common [7,19–23,26]. In our hospital in 1991, 100% of the *A. baumannii* isolates in blood were susceptible to imipenem, whereas in the year 2000, 50% were resistant to this antimicrobial. Urban et al. previously described the appearance of imipenem resistance following the increased use of this antimicrobial to treat an outbreak of nosocomial infections by *Acinetobacter* sp. The isolates of imipenem-resistant *A. baumannii* are often multidrug resistant [27].

The development of resistance to antimicrobials in *A. baumannii* appears to be unstoppable. In 1993 five isolates, two in blood, which were only resistant to colistin were described [28]. These data are disturbing because the therapeutic possibilities decrease while patient mortality increases with inappropriate antimicrobial treatment [7,29].

PROGNOSIS

In general, *A. baumannii* bacteremia is associated with a high crude mortality rate, but it is difficult to distinguish between morbidity and mortality attributable to *A. baumannii* and that attributable to comorbidity, which is common and severe in these patients.

The data from some prognostic studies on ICU patients suggest that infection by *A. baumannii*, particularly pneumonia, increases mortality and prolongs hospital stay [30–32].

However, the prognosis of bacteremia by *A. baumannii* is still unclear. Previous studies, including the one carried out by our group, confirm that the crude mortality rate is high, fluctuating between 17% and 52%; and the factors independently associated with poor prognosis are the

severity of the underlying disease, pneumonia as the source of bacteremia, septic shock, disseminated intravascular coagulation, mechanical ventilation, and inappropriate antimicrobial treatment [5–9]. In contrast, bacteremias originating from vascular catheters and bacteremias caused by non-*baumannii Acinetobacter* were associated with lower mortality [7,18,33,34]. The preliminary results of a prospective study of cases and controls aiming to establish a prognosis for nosocomial *A. baumannii* bacteremia suggest that high mortality in these patients is not due to the bacteremia, but to co-morbidity, whereas prolonged hospital stay is related to the bacteremia itself [35].

TREATMENT

The treatment of choice for *A. baumannii* bacteremia has not been established. There have been no comparative therapeutic trials, and clinical experience is lacking. The usual treatment is an active β-lactam alone or an association with to an aminoglycoside, similar to the treatment for bacteremia caused by other Gram-negative bacilli [25].

Imipenem treatment resulted in cure of the bacteremia in 83% of the cases in one study [7]. There are no clinical studies comparing the efficiency of monotherapy with a β-lactam and therapy in combination with an aminoglycoside. Synergy between an imipenem β-lactam inhibitor and an aminoglycoside has been reported in the in vitro studies [36]. However, experimental studies suggest that the addition of aminoglycoside does not improve the results obtained by imipenem monotherapy. Rodríguez-Hernández et al. reported that monotherapy with imipenem is as effective as therapy with imipenem plus amikacin in the treatment of experimental *A. baumannii* pneumonia [37].

Sulbactam is an inhibitor of β-lactamase, which shows in vitro bactericidal activity against *Acinetobacter* sp. [38–41]. Rodríguez-Hernández et al. showed that the efficacy of sulbactam in experimental infections caused by susceptible *A. baumannii* strains was similar to that of imipenem [42]. Serum and cerebrospinal fluid levels (in patients with meningitis) of sulbactam average 68 mg/L and 8.5 μg/mL, respectively, when 1 g is given intravenously. Sulbactam has initially been used along with ampicillin in the treatment of 10 patients with infections caused by *Acinetobacter* sp. resistant to imipenem, nine of whom improved clinically [27]. Corbella et al. treated 42 patients with non-life-threatening multiresistant *A. baumannii* infections, including seven bacteremias, with sulbactam alone and in combination with ampicillin (1 g every 8 h); 39 improved or were cured with no major adverse affects. In this study, killing curves showed that sulbactam was bacteriostatic [43]. Also, sulbactam may be effective as therapy for bacteremia with meningitis caused by multidrug-resistant *A. baumannii*. Jiménez-Mejías et al. cured six out of eight patients with nosocomial *A. baumannii* meningitis treated with sulbactam (1 g every 6–8 h) [44]. One retrospective analysis compared treatment outcomes of 48 patients with *A. baumannii* bacteremia treated with imipenem or ampicillin–sulbactam. Ampicillin–sulbactam was at least as effective as imipenem and was a cost-effective alternative for treatment [45]. Finally, we described the cure of seven out of eight patients (87%) with *A. baumannii* bacteremia following treatment with sulbactam [7]. These data support the recommendation of sulbactam treatment (1 g given intravenously each 6–8 h for 10–14 days) for *A. baumannii* bacteremia whenever the organism is susceptible to this antimicrobial (Table 1).

Unfortunately, resistance to sulbactam has been noted in imipenem-resistant strains of *A. baumannii*, leaving the polymyxins (colistimethate and polymyxin B) as the only treatment alternative [28]. Colistin was used in the 1960s and 1970s but was abandoned due to adverse side-effects, mainly nephrotoxicity, neurotoxicity and neuro-

Table 1 Antimicrobials recommended for the treatment of bacteremia due to *A. baumannii*

Bacteremia due to non-multiresistant *A. baumannii*
an active betalactam according to antibiogram, preferably one with reduced spectrum (example: sulbactam > aztreonam > ceftazidime > imipenem)
Bacteremia due to multiresistant *A. baumannii*
Choice: sulbactam 1 g intravenously every 6–8 h
Alternative: imipenem 500 mg intravenously every 6 h (multiresistant *Acinetobacter* spp. is habitually only susceptible to imipenem)
If meningitis-associated: meropenem 1 g intravenously every 8 h
Bacteremia by imipenem-resistant *A. baumannii*
Sulbactam 1 g intravenously every 6–8 h
Bacteremia by 'pan-resistant' *A. baumannii*
Colistin 2.5–5 mg/kg/day intravenously in two or three doses

muscular blockage, and because of the emergence of newer and safer antimicrobials. Through a poorly understood mechanism of action, colistin breaks the bacterial wall and is active against many Gram-negative bacteria, but not against Gram-positive rods. Colistin scarcely penetrates through the blood–brain barrier. Go et al. first used polymixin B, applied topically, in the treatment of infections by imipenem-resistant *A. baumannii*. Infection and colonization were eliminated by intensive infection control measures, and irrigation of wounds with polymixin B [46]. Levin et al. reported the outcomes of 60 nosocomial infections, including bacteremia, caused by *A. baumannii* and *Pseudomonas aeruginosa* which were resistant to all commercially available antimicrobial agents, treated with colistin [47]. The patients were treated with 2.5–5.0 mg of colistin/kg daily up to a maximum dose of 300 mg, which was divided into two or three intravenous doses. When the patients presented with renal failure, the daily dose was adjusted: serum creatinine level from 1.3 to 1.5 mg/dL, daily dose of 2.5–5.0 mg/kg; 1.6–2.5 mg/dL, 2.5 mg/kg; and >2.5 mg/dL, 1.0–1.5 mg/kg. The mean duration of treatment was 14 days (5–25 days). There was a good outcome for 58% of the patients in general, but for only 25% of the patients with pneumonia. The main adverse effect of treatment was renal failure (27% in patients with initially normal renal function, and 58% in patients with initially abnormal renal function), however treatment was not discontinued because of nephrotoxicity and no neuromuscular disorders were observed.

The results of this study make it possible to recommend colistin (2.5–5 mg/kg/day intravenously for 14 days) for treating patients with *A. baumannii* bacteremia who have no other therapeutic options. It is necessary to adjust the dose for patients with altered renal function and to monitor them closely.

Other in vitro studies showed that rifampicin in conjunction with either colistin or sulbactam was synergic against multidrug-resistant strains of *A. baumannii*, and suggest that that combination may be effective therapy for patients with severe infections caused by multidrug-resistant strains of *A. baumannii* [48,49].

Before beginning treatment of an *A. baumannii* bacteremia, it is very important to carry out a clinical evaluation of the patient to eliminate the possibility of a pseudobacteremia, diagnosed due to incorrect collection or handling of the blood culture, and thereby avoid unnecessary treatment. Furthermore, it is important to try to establish the origin of the bacteremia, making its elimination possible. Removal of the intravascular catheter, or other foreign body, and surgical treatment of the source of the bacteremia whenever possible, are indicated.

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