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Clinical epidemiology and resistance mechanisms of carbapenem-resistant *Acinetobacter baumannii*, French Guiana, 2008–2014

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ABSTRACT

This study investigated the clinical epidemiology and resistance mechanisms of *Acinetobacter baumannii* and characterised the clonal diversity of carbapenem-resistant *A. baumannii* (CRAB) during an ICU-associated outbreak at Cayenne Hospital, French Guiana. All non-duplicate *A. baumannii* isolates from 2008 to 2014 were tested for antibiotic susceptibility by disk diffusion. Multilocus sequence typing, pulsed-field gel electrophoresis (PFGE) and characterisation of carbapenemase-encoding genes were performed on CRAB. Of the 441 *A. baumannii* isolates, most were from males (54.0%) and were detected mainly from the ICU (30.8%) and medicine wards (21.8%). In the ICU, strains were mainly isolated from the respiratory tract (44.1%) and bloodstream (14.0%), whereas in medicine wards they mainly were from wound/drainage (36.5%) and bloodstream (25.0%). *A. baumannii* showed the greatest susceptibility to piperacillin/tazobactam (92.7%), imipenem (92.5%), colistin (95.6%) and amikacin (97.2%), being lower in the ICU and medicine wards compared with other wards. An outbreak of OXA-23-producing CRAB occurred in the 13-bed ICU in 2010. CRAB strains were more co-resistant to other antimicrobials compared with non-CRAB. Molecular genetics analysis revealed five sequence types [ST78, ST107 and ST642 and two new STs (ST830 and ST831)]. Analysis of PFGE profiles indicated cross-transmissions of CRAB within the ICU, between the ICU and one medicine ward during transfer of patients, and within that medicine ward. This study provides the first clinical and molecular data of *A. baumannii* from French Guiana and the Amazon basin. The ICU was the highest risk unit of this nosocomial outbreak of OXA-23-producing CRAB, which could subsequently disseminate within the hospital.

1. Introduction

Acinetobacter baumannii is a lactose-non-fermenting, Gram-negative coccobacillus and an opportunistic pathogen of the skin and respiratory tract of inpatients. Community-acquired *A. baumannii* infections have been reported, but few strains have been recovered from environmental sources, and infection reservoirs outside of the hospital have not been clearly identified. Another relatively recent phenomenon has been the association of *A. baumannii* with infections following unusual situations, such as infections in victims of earthquakes or with war-related wounds in Iraq and Afghanistan [1,2].

A. baumannii has emerged over the last decades as a major cause of healthcare-associated infections [3], causing a wide range of nosocomial infections occurring either sporadically or as outbreaks, mainly in intensive care units (ICUs), and including ventilator-associated pneumonia, bloodstream infections, urinary tract infections, wound infections, skin and soft-tissue infections and, rarely, meningitis, endocarditis and endophthalmitis [4–6]. It is often difficult to distinguish colonisation from true *A. baumannii* infection, and the colonised or infected patient appears to be the primary reservoir of pathogenic *A. baumannii*.

Factors facilitating the transmission of *A. baumannii* include contamination of the hospital environment, prolonged hospitalisation,

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prior antibiotic exposure, presence of invasive devices, underlying pathologies and poor adherence to hand hygiene practices [7–9].

A. baumannii is also known for its ability to develop resistance to multiple classes of antibiotics, which has been an important factor in the increased recognition of the clinical significance of this organism [6,10]. Carbapenem resistance is considered a significant health problem because of the limited options for antibiotic treatment and it is now observed worldwide [10,11].

In French Guiana and the Amazon basin, data on the clinical features, antibiotic susceptibility and molecular genetics of *A. baumannii* are scarce. The objectives of this study were to investigate the clinical epidemiology and resistance mechanisms of *A. baumannii* and to study the clonal diversity and enzymes of carbapenem-resistant *A. baumannii* (CRAB) during an outbreak in the ICU at the Centre hospitalier Andrée Rosemon (CHAR), Cayenne, French Guiana.

2. Materials and methods

2.1. Setting

French Guiana is a French overseas territory located in the tropics on the north-eastern coast of South America between Brazil and Suriname. Cayenne, the capital city, accommodates almost 50% of the 215,000 inhabitants living in French Guiana. CHAR, the main hospital of Cayenne, is a 603-bed tertiary care hospital, including 503 acute-care beds (in internal medicine, surgery, obstetrics/gynaecology, neonatology, paediatrics and the ICU), 30 intermediate-term care beds (in units receiving patients who require convalescence or physical therapy) and 70 long-term care beds.

2.2. Isolates

All non-duplicate *A. baumannii* isolates collected from clinical specimens of patients >48 h following their hospital admission between January 2008 and December 2014 were included in this study. For each isolate included, the following data were collected: patient age and sex; hospitalisation unit; site of infection or colonisation; and antibiotic susceptibility. Identification of *A. baumannii* isolates was based on conventional techniques as well as automated instruments including VITEK®2 (bioMérieux, Marcy-l'Étoile, France), API 20 NE method (bioMérieux) and, recently, matrix-assisted laser desorption/ionisation time-of-flight mass spectrometry (MALDI-TOF/MS) (Bruker Daltonics, Wissembourg, France). Before 2013, no molecular technique was used to differentiate between species belonging to the so-called *A. baumannii* complex. However, the denomination of *A. baumannii* is used throughout the text for clarity, as done by other authors [12].

2.3. Antibiotic susceptibility testing

Susceptibility testing was performed by the disk diffusion method on Mueller–Hinton agar (bioMérieux). Antibiotic susceptibility results were interpreted according to CLSI (Clinical and Laboratory Standards Institute) standards [13]. For imipenem-resistant isolates, imipenem minimum inhibitory concentrations (MICs) were determined by Etest (bioMérieux, La Balme-les-Grottes, France) according to the manufacturer's recommendations.

2.4. Molecular genetics analysis

Carbapenem-resistant *A. baumannii* (CRAB) isolates (imipenem MIC > 4 μg/mL; CLSI breakpoint) stored at the microbiology laboratory were thawed for subsequent identification and for the detection of the naturally occurring OXA-type β-lactamase genes ($bla_{\text{OXA-51}}$ and its variants) [14]. A multiplex PCR assay was used to detect known OXA carbapenemase genes grouped into four sequence clusters ($bla_{\text{OXA-23-like}}$, $bla_{\text{OXA-24/40-like}}$, $bla_{\text{OXA-58-like}}$ and $bla_{\text{OXA-51}}$) [15]. Detection of $bla_{\text{OXA-143}}$ was performed by a separate PCR [16]. The presence of genes for Ambler class A (PER, GES and VEB) and class B carbapenemases (IMP, VIM and NDM) was investigated as described previously [17]. The insertion sequence element IS*Aba1* upstream of the $bla_{\text{OXA-51}}$ gene was searched for by PCR. Amplicons were sequenced on both strands on a 3100 DNA sequencer (PE Applied Biosystems, Foster city, CA) and sequences were compared with those in public databases.

Pulsed-field gel electrophoresis (PFGE) with the restriction enzyme *Apa*I (Roche Diagnostics, Meylan, France) was performed and profiles were interpreted according to international recommendations [18]. A cluster was defined as two or more cases occurring in a time period and location where cross-transmission was suspected. Multilocus sequence typing (MLST) was performed using the method of the Institut Pasteur [19] (http://www.pasteur.fr/mlst). Clonal complexes were defined as groups of sequence types (STs) differing by a single allelic mismatch with at least one other ST of the group.

2.5. Ethics statement

Patients' medical records were retrospectively reviewed and all data collected were anonymised in standardised forms according to procedures of the Commission nationale de l'informatique et des libertés (the French Information Protection Commission).

2.6. Statistical analyses

Categorical variables were summarised as percentages and were compared using Fisher's exact test. Continuous variables were summarised as mean ± standard deviation or median and interquartile ranges (IQR) and were compared using the Mann–Whitney test. Evolving trends of antibiotic resistance of *A. baumannii* over time were assessed using the Cochran–Armitage test for linear trend. Statistical analyses were performed using SAS software v.8.01 (SAS Institute Inc., Cary, NC). A *P*-value of <0.05 was considered statistically significant.

3. Results

3.1. Isolates

From January 2008 to December 2014, a total of 441 non-duplicate *A. baumannii* strains isolated from inpatients at CHAR were analysed. Of these, 238 (54.0%) were from males and the median age was 39.8 years (IQR 23.9–54.3 years). *A. baumannii* isolation significantly increased with age, from 27.7% in patients <25 years old to 42.1% in those aged >45 years ($P < 0.001$). *A. baumannii* most commonly infected/colonised critically ill patients from the ICU (30.8%), followed by patients from medicine wards (21.8%). Isolates were mainly from wound/drainage and skin and soft-tissue (26.3%), bloodstream (18.4%), urinary tract (16.8%) or respiratory tract (16.1%). In ICU patients, *A. baumannii* strains were mainly isolated from the respiratory tract (44.1%), bloodstream (14.0%) and vascular catheters (10.3%), whereas in medicine wards they were isolated mainly from wound/drainage (36.5%), bloodstream (25.0%) and the urinary tract (24.0%) (Table 1).

3.2. Antibiotic susceptibility

The antibiotic susceptibilities of the *A. baumannii* isolates are shown in Table 2. Overall, *A. baumannii* isolates showed high susceptibility to piperacillin/tazobactam (TZP) (92.7%), imipenem (92.5%), colistin (95.6%) and amikacin (97.2%). From 2008 to 2014, a steadily increasing trend of resistance was observed for cefepime,

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