Successful management of nosocomial ventriculitis and meningitis caused by extensively drug-resistant *Acinetobacter baumannii* in Austria

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Nosocomial infections caused by the Gram-negative coccobacillus *Acinetobacter baumannii* have substantially increased over recent years. Because *Acinetobacter* is a genus with a tendency to quickly develop resistance to multiple antimicrobial agents, therapy is often complicated, requiring the return to previously used drugs. The authors report a case of meningitis due to extensively drug-resistant *A. baumannii* in an Austrian patient who had undergone neurosurgery in northern Italy. The case illustrates the limits of therapeutic options in central nervous system infections caused by extensively drug-resistant pathogens.

Key Words: *Acinetobacter baumannii*; Colistin; Meningitis; Multidrug resistance

CASE PRESENTATION

A 66-year-old Austrian woman was transferred from an intensive care unit in northern Italy to the neurosurgical intensive care unit of the Medical University of Graz hospital in Graz, Austria. The patient had experienced a subarachnoid hemorrhage due to a ruptured aneurysm in the anterior communicating artery during a holiday stay in northern Italy, at which time she had been admitted to a neurosurgical ward. The aneurysm was clipped and an external ventricular drain (EVD) was inserted on the left side. Reports from Italy revealed that the patient had developed nosocomial pneumonia during the two-week hospital stay. Methicillin-resistant *Staphylococcus aureus* was cultured from bronchoalveolar lavage fluid and intravenous vancomycin was initiated.

On admission to hospital, the patient was able to open her eyes spontaneously and made uncoordinated movements with her upper limbs. Babinski sign was positive. Blood work revealed elevated neutrophil and C-reactive protein (CRP) levels (neutrophils 86%, normal range <75%; neutrophil absolute count $7.1 \times 10^9/L$; CRP 49.8 mg/L, normal range <8 mg/L), anemia (red blood cell count $2.63 \times 10^{12}/L$, hemoglobin 75 g/L, hematocrit 23.1%) and an electrolyte imbalance (sodium 150 mmol/L, potassium 3 mmol/L). The next day, meropenem 1 g every 8 h was initiated empirically in addition to vancomycin due to fever and increasing CRP level.

A lumbar puncture was performed. Cytology of cerebrospinal fluid (CSF) revealed 781 cells/ μL and inflammation dominated by neutrophils with intracellular coccobacilli. Additional monocytes, activated monocytes and lymphocytes were found; glucose level was <0.62 mmol/L and protein level was 1300 mg/L. Extensively drug-resistant *Acinetobacter baumannii* was cultured from CSF.

La prise en charge réussie d'une ventriculite et d'une méningite d'origine nosocomiale causées par un *Acinetobacter baumannii* d'une extrême résistance aux médicaments en Autriche

Les infections d'origine nosocomiale causées par le coccobacille *Acinetobacter baumannii* Gram négatif ont considérablement augmenté ces dernières années. Puisque l'*Acinetobacter* est un genre qui a tendance à devenir rapidement résistant à de multiples agents antimicrobiens, le traitement est souvent compliqué et exige de revenir à des médicaments déjà utilisés. Les auteurs signalent un cas de méningite attribuable à un *A. baumannii* d'une extrême résistance aux médicaments chez un patient autrichien qui a subi une neurochirurgie dans le nord de l'Italie. Le cas illustre les limites des options thérapeutiques aux infections du système nerveux central causées par des pathogènes d'une extrême résistance aux médicaments.

Antimicrobial susceptibility testing was performed using Etest (AB bioMérieux, Sweden) and showed susceptibility to colistin only (minimum inhibitory concentration [MIC] 0.125 mg/L) (1); for tigecycline (MIC 2.0 mg/L), interpretation was inferred from available breakpoints for *Enterobacteriaceae* issued by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) (susceptible MIC <1 mg/L, resistant MIC >2 mg/L) (2).

Antimicrobial synergy testing was performed using the relevant Etest method (3). Synergy was defined as a fractional inhibitory concentration index (FIC) <0.5 (4) and was found for the combinations colistin/ciprofloxacin (FIC 0.0679) and for tigecycline/meropenem (FIC 0.25). The FIC of colistin/tigecycline was 1.28 (ie, indifferent).

Meropenem was continued and additional anti-infective therapy with tigecycline 50 mg every 12 h and fosfomycin 8 g every 8 h was initiated. Neutrophil count and CRP levels subsequently decreased; however, they relapsed, procalcitonin (PCT) level was elevated (1.38 $\mu g/L$; normal range <0.5 $\mu g/L$), and the patient became febrile again. In subsequent CSF specimens, *A. baumannii* was repeatedly isolated. Therefore, therapy was changed to intrathecal colistin – 1.6 mg on the first day, and subsequently increased by 1.6 mg per day until 8 mg per day was reached, consistent with previously published recommendations (5). Due to synergy testing results, ciprofloxacin 400 mg every 8 h was added; all other anti-infective agents were discontinued.

Neutrophil count, PCT and CRP levels decreased, and the EVD was changed. After three days, however, the patient's condition deteriorated; she developed somnolence, her temperature increased to 40°C and she developed hemodynamic instability. PCT and CRP levels increased significantly (CRP to 183 mg/L, PCT to 1.78 $\mu g/L$, normal range <0.5 $\mu g/L$) and the identical *A. baumannii* isolate that was

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repeatedly recovered from CSF was now also cultured from tracheal secretions. Intravenous antimicrobial therapy with colistin 240 mg every 12 h (due to colonization of the tracheobronchial tree with the same *A baumannii* strain) and linezolid 600 mg every 12 h (persistent methicillin-resistant *S aureus* colonization) was initiated in addition to ciprofloxacin and intrathecal colistin.

Under this regimen, the patient stabilized slowly. Intrathecal colistin was tolerated well and the patient did not develop seizures.

After three weeks in hospital, the CSF became, for the first time, culture negative. Intrathecal colistin was discontinued after 17 days of treatment as was ciprofloxacin. Therapy with intravenous colistin and linezolid was continued for four days after discontinuation of intrathecal colistin. A ventriculoperitoneal shunt was placed after six weeks in hospital. *A baumannii* was detectable in urine and stool until the end of the hospital stay. After 64 days in hospital, the patient was discharged into rehabilitation.

DISCUSSION

We report a case of EVD-associated meningitis caused by extensively drug-resistant *A baumannii* in a critically ill patient. To our knowledge, the present article describes the first reported case of meningitis caused by multidrug-resistant *A baumannii* in Austria.

The Gram-negative coccobacillus *A baumannii* has frequently been reported to cause a number of nosocomial infections including ventilator-associated pneumonia, bloodstream infections, urinary tract infections and secondary meningitis (6-10). According to some studies, the occurrence of *A baumannii* is correlated with a higher rate of mortality and longer hospital stay (11). Meningitis caused by *A baumannii* may appear after neurosurgical procedures, particularly those that involve prolonged external ventricular drainage (9,12). Another risk factor is the prolonged use of broad-spectrum antimicrobial agents in neurosurgical intensive care units (7). Both of these risk factors applied to our patient. The mortality rate of *A baumannii* meningitis ranges from 15% to 71% (13).

Over the past years, *Acinetobacter* has gained increasing importance due to therapeutic difficulties in treatment. As a result of the various resistance mechanisms (including beta-lactamases, efflux pumps and alterations in cell wall channels), *Acinetobacter* has become resistant to the vast majority of available antibiotics (6,13-15). Due to its ability to quickly adapt to its environment, the frequency of hospital-acquired infections due to *Acinetobacter* species has increased significantly over recent decades (16). Limited penetration of antibiotics to achieve therapeutic concentrations in CSF poses an additional problem in central nervous system infections (16-18). *A baumannii* resistance is a recognized problem worldwide; the WHO has recognized antimicrobial resistance as one of the three most important problems to human health (19) and has registered *A baumannii* as a nosocomial pathogen in which resistance is of great public health concern (20).

In 2004, Kresken et al (21) analyzed antibiotic susceptibility of clinical *A baumannii* isolates from Austria, Germany and Switzerland, and found that meropenem was the most active compound against *A baumannii*, followed by imipenem, doxycycline and tobramycin. Ciprofloxacin was active against 78% of isolates.

In our case, a combination of intrathecal colistin and intravenous ciprofloxacin was used for treatment of the infection after susceptibility testing had shown low MICs for this combination therapy. Thereafter, therapy was modified to intrathecal and intravenous colistin for central nervous system and concomitant respiratory tract infection caused by the extensively drug-resistant strain. Studies have shown that the combination of intravenous and intrathecal colistin is effective against meningitis caused by *A baumannii* (5,22-24). Rodriguez Guardado et al (25) reported 51 cases of nosocomial postsurgical meningitis due to *A baumannii*. In that study, the combination of intravenous and intrathecal colistin was a safe and useful option for the treatment of *Acinetobacter* meningitis. Khawcharoenporn et al (26) suggested that intrathecal colistin therapy is as efficacious as either primary or adjunct treatment. De Pascale et al (27) reported a case

involving a 42-year-old man with postneurosurgical ventriculitis caused by *A baumannii* who was cured using treatment with intrathecal colistin.

Therefore, we conclude that a combination of intrathecal and intravenous colistin may be an effective therapeutic option in the treatment of extensively drug-resistant *A baumannii* meningitis. Furthermore, the present case illustrates the urgent need for new anti-infective agents for treatment of extensively drug-resistant bacterial strains such as the strain described in the present report.

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