Rare disease

Multidrug-resistant *Acinetobacter baumannii* infection in children

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Summary

Acinetobacter baumannii is a Gram-negative coccobacillus causing serious nosocomial infections. The recent emergence of strains of bacteria, which are resistant to common antibiotics, has made the treatment of these infections increasingly complex. We report the case of a young patient affected by AIDS, who suffered brain toxoplasmosis and sepsis due to multidrug-resistant *A baumannii*. This bacterial infection was successfully treated with colistin and tigecycline. In addition, we review recent literature on this topic, from the year 2000 to date.

BACKGROUND

Acinetobacter baumannii is a Gram-negative coccobacillus, which is widespread in nature and has emerged as an important nosocomial pathogen in recent years, especially in intensive care units (ICUs).¹ The incidence of *A baumannii* infections has increased during the past decades, probably because of a rise in the proportion of the population susceptible to infections, as a result of advancement in the treatment of critically ill patients.

Affected patients often have specific characteristics such as old age, serious underlying diseases, immunosuppression, have suffered major traumas or burn injuries, have been subject to invasive surgical procedures including indwelling catheters, support with mechanical ventilation, extended hospital stay or previous administration of antibiotics.

In the past, the main therapeutic options were carbapenems (especially meropenem), used in isolation or in combination with amikacin. However, in recent years, there has been a substantial increase in the rates of antibiotic resistance of *A baumannii*. As a result, fewer therapeutic options are now available, including combinations of antimicrobials such as rifampicin, ampicillin/sulbactam, aminoglycoside, tigecycline, colistin and carbapenems.¹

Moreover, the treatment of such severe infections in the paediatric population is rarely described in the literature.

Here, we report the case of a child affected by a multidrug-resistant *A baumannii* infection, which was successfully treated with tigecycline and colistin. We further discuss this case in relation to all the published cases of *A baumannii* infections in the paediatric population collected through a MEDLINE search of the international literature from 2000 to date.

CASE PRESENTATION

A 12-year-old boy with negative physiological and pathological history was admitted in a rural African hospital

for headache and weakness. A brain MRI scan evidenced lesions occupying space and hydrocephalus. Suspecting that the child was affected by lymphoma, a ventriculoperitoneal shunt was successfully applied with a subsequent reduction of intracranial hypertension. Since a blood count revealed severe lymphopenia, a HIV ELISA test was performed, with a positive result. Antiretroviral treatment was started. Due to the severe immunosuppression (CD4 1%), positive serology against toxoplasma and MRI results, brain toxoplasmosis was diagnosed and specific treatment with pyrimethamine plus clindamycin and folinic acid was started according to the availability of local drugs.

During the following 3 days, the child's respiratory functions progressively worsened, which required mechanical ventilation for 5 days. *Pneumocystis jirovecii* pneumonia was suspected and specific treatment with trimethoprim/sulfamethoxazole and dexamethasone was started. The treatment led to a progressive improvement of the lung function. Because of the severe immunodeficiency and the multiple concomitant opportunistic infections, the child was transferred to our attention.

On admission in our Ward, physical examination revealed critical general condition, fever (38.5°C), wasting syndrome and hepatosplenomegaly. Neurological examination found drowsiness, aphasia, right hemiparesis and diffused muscle atrophy. The Glasgow coma score was 7. The child's weight was 30 kg.

After 2 days of hospitalisation, the patient reported suprapubic pain, especially during urination.

INVESTIGATIONS

Upon admission, blood examination showed white cell count $5.34 \times 10^3/\text{ul}$ with 74.3% neutrophils and 16.5% lymphocytes (CD4 count $27.3/\text{mm}^3 - 3.1\%$), C reactive protein 26.9 mg/dl, international normalised ratio 2.1% and HIV viral load 570 copies/ml. Due to a bilateral vesicular murmur reduction, a chest x-ray was performed, which

Table 1 Cases of multidrug-resistant *Acinetobacter baumannii* infections occurring in our hospital in the last 4 years

Patient	Sex	Age	Underlying condition	Diagnosis	Isolation	Regimen used	Duration	Toxicity	Duration of hospitalisation	Outcome
1	M	12 years	AIDS, brain toxoplasmosis	Sepsis and meningitis	Peritoneal swab/CSF	Colistin and tigecycline	4 weeks	None	77 days	Discharged
2	F	16 months	Burns	Sepsis and septic shock	Arterial catheter	Meropenem	n/k	None	32 days	Discharged
3	M	3 years	Hypoxic ischaemic encephalopathy and recurrent pneumonia, tracheostomy	VAP	Tracheal aspirate	Meropenem and amikacin	n/k	None	53 days	Discharged
4	F	15 years	Charcot-Leiden syndrome, tracheostomy	VAP	Tracheal aspirate	Meropenem and amikacin	n/k	None	33 days	Discharged
5	M	21 years	Spastic quadriplegia, tracheostomy	VAP	Tracheal aspirate	Colistin and meropenem	n/k	None	94 days	Discharged
6	M	16 years	Adrenoleucodystrophy, tracheostomy	VAP	Tracheal aspirate	Colistin	3 weeks	None	58 days	Discharged
7	F	15 years	Metabolic disease, tracheostomy	VAP	Tracheal aspirate	Meropenem and amikacin	1 week	None	50 days	Discharged
8	F	25 years	Spastic quadriplegia, tracheostomy	VAP	Tracheal aspirate	Colistin and meropenem	4 weeks	None	179 days	Discharged

n/k, not known.

showed a left pleural effusion. Epstein–Barr virus and cytomegalovirus infection was ruled out on the basis of a molecular test (PCR).

Brain CT documented coarse, hypodense and inhomogeneous area, probably due to toxoplasmosis, localised in the left basal ganglia. Other hypodense areas of variable size were diffused bilaterally in all brain parenchyma. Electroencephalogram showed diffuse depressed brain activity, without epileptiform abnormalities.

After the onset of suprapubic pain, an abdominal ultrasound scan was performed, which visualised fluid collection (37×34×66 mm) of probable infectious origin above the bladder located in the point of insertion of the ventricular-peritoneal shunt.

The most likely cause of the clinical status of the patient was a meningitis secondary to neurosurgery, which was complicated by the contamination of the shunt with consequent formation of a peritoneal abscess and sepsis. Indeed, ventriculo-peritoneal catheter culture, cerebrospinal fluid (CSF) examination and peritoneal swab culture revealed the presence of multidrug-resistant (MDR) *A baumannii*. The bacteria were identified by morphology, Gram stain and reactions with automated instrument Vitek 2 (BioMerieux, Inc.100 Rodolphe Street, Durham, NC 27712).

Full in vitro antibiotic susceptibility was exclusively present for colistin (minimum inhibitor concentration (MIC) 1.5 mg/l) and tigecycline (MIC 0.5 mg/l) with a partial susceptibility to amikacin, tobramycin and levofloxacin.

TREATMENT

At the beginning, antibiotic treatment with meropenem and piperacillin/tazobactam was started.

Successively, vancomycin was added to the treatment, following the discovery of the fluid collection above the bladder.

Since culture results detected the presence of MDR *A baumannii*, the patient was treated with a combined therapy based on the association of colistin (150 000 UI/kg/day divided in three doses) and tigecycline (3 mg/kg/day divided in two doses) for 4 weeks and then continued with tigecycline alone for another 4 weeks. Therapy was well

tolerated. At the same time, highly active antiretroviral therapy treatment led an increase of CD4 cells (126 cells/ml – 5.1%).

OUTCOME AND FOLLOW-UP

The patient's general clinical conditions rapidly improved and there was a reduction of the inflammation markers, with a complete disappearance of fever after 1 week of therapy. After 2 weeks of therapy, CSF testing gave a negative result. Successive chest x-ray showed gradual improvement of pleural effusion. The successive programme of rehabilitation led to an improvement of the neurological symptoms with partial recovery of right hemiparesis. The patient was discharged from hospital after 75 days, with a programme to continue rehabilitation. He has now completely recovered and can stand up alone, walk and make motor coordination exercises.

DISCUSSION

MDR *A baumannii* is defined by the presence of resistance to carbapenems or to at least three classes of antimicrobials.^{2–4}

Our experience in treating infections caused by MDR bacteria is based on a cohort of eight patients, observed during the period between 2007 and 2010, including the case reported here (see table 1). Every patient presented with a risk factor: hospitalisation in intensive care (7), tracheostomy (6), arterial catheter (1) or ventricular-peritoneal shunt (1). Clinical manifestations were sepsis, sepsis and meningitis, and pneumonia. Patients were treated with carbapenems, in monotherapy (1) or in association with amikacin (3), or colistin, alone (1) or in association with meropenem (2) or tigecycline (in the patient described earlier). The mean duration of hospitalisation was 72 days. All treatments had a good outcome.

A review of the literature was performed by a PubMed search for the period between January 2000 and November 2010 to find cases similar to ours. A study was considered eligible for inclusion in the review if it reported paediatric data on the localisation of the disease, isolation of the bacterium, type duration and safety of the antibiotic

Table 2 Case reports of *Acinetobacter baumannii* infections in children, previously described in literature

References (authors) (year)	Age	Sex	Underlying condition	Diagnosis	Isolation	Regimen used	Dosage of colistin intravenous	Duration (days)	Toxicity	Outcome
Ozdemir (2010) ¹	3 years	F	Choroid plexus papilloma	Meningitis	CSF	Colistin intravenous + intrathecal	50 000 IU/kg/day divided q 8 h	45	None	n/k
	14 years	F	Medulloblastoma	Meningitis	CSF	Meropenem + ampicillin/subactam + rifampicin	n/k	28	None	n/k
	14 months	M	Congenital hydrocephalus	Meningitis	CSF	Meropenem + colistin intravenous	50 000 IU/kg/day divided q 8 h	42	None	n/k
Ozaki (2009) ¹²	14 months	M	Healthy patient	Meningitis	CSF	Meropenem	n/k	19	None	No sequela
Dalgic (2009) ¹³	2 months	F		Meningitis	CSF	Colistin intravenous + intrathecal	5 mg/kg/day	20 days intravenous + 7 days intravenous and intrathecal	None	n/k
Falagas (2009) ⁷	13 years	M	Healthy patient → accident	Infection of lower respiratory tract	Bronchial aspirate	Colistin + piperacillin/tazobactam	5 mg/kg/day divided into three doses	10	None	n/k
	14 months	M	GM1 gangliosidosis	Sepsis	Blood	Colistin + imipenem	5 mg/kg/day divided into three doses	10	None	n/k
	11 years	M	Healthy patient → accident	Infection of lower respiratory tract	Bronchial aspirate	Colistin + vancomycin	5 mg/kg/day divided into three doses	10	n/k	Improved from infection but died due to different causes
Mukhopadhyay (2008) ¹⁴	18 years	M	Healthy patient → accident	VAP	Tracheal aspirate	Colistin + meropenem	1.5 mg/kg q 8 h	14	n/k	n/k
Lee (2008) ¹⁵	3 years	M	Medulloblastoma	Meningitis and sepsis	CSF and blood	Colistin intravenous	5 mg/kg/day	28	None	n/k
Biancofiore (2007) ¹⁶	16 years	F	Healthy patient → accident	Multifocal infection (lung, skin, soft tissue)	Skin graft, CVC, BAL	Colistin + meropenem	2 ml UI/twice/day	70	n/k	n/k
NG (2006) ¹⁷	4 years	M	Medulloblastoma	Meningitis	CSF and blood	Colistin intrathecal	n/k	39	Toxic meningitis due to colistin	n/k
Kendirli (2004) ¹⁸	3 months	F	Myelomeningocele	Meningitis	CSF	Ampicillin/sulbactam	n/k	17	n/k	n/k
Jiménez-Mejías (2002) ¹⁹	14 years	M	Healthy patient → accident	Meningitis	CSF	Colistin intravenous	1 ml UI × 3 times/day	30	None	n/k

treatment, and outcome of paediatric patients with infections caused by MDR *A baumannii*.

Our search identified 10 relevant articles, describing overall 14 children (five girls and nine boys), with mean age 7.1 years. Data concerning these patients are shown in table 2. Risk factors were present in all patients. Clinical manifestations were meningitis (8), meningitis and sepsis (1), sepsis (2) and ventilator-associated pneumonia (VAP) (3). Concerning the treatment, colistin was the final therapeutic regimen in 11/14 patients; route of administration was intravenous, combined with intrathecal administration in three patients affected by meningitis. Colistin was used in monotherapy just in four cases. Combined therapy provided the association of colistin with meropenem (5) or piperacillin/tazobactam (1). In one patient colistin was combined with vancomycin, although it is well known that glycopeptides are not active on most Gram-negative bacteria. Patients who did not use colistin were treated with meropenem in monotherapy (1) or in association with ampicillin/sulbactam and rifampicin (1), or ampicillin/sulbactam alone (1). There was considerable variability in the duration of treatment; therapy lasted on average 27.8 days (from a minimum of 10 days in the milder forms to a maximum of 70 days in the very severe cases). The most used dosing scheme of colistin was 4–5 mg/kg/day in three doses. Toxicity probably related to administration of colistin was reported in just one patient, where colistin caused toxic meningitis, evidenced by the appearance of CSF leukocytosis.

Analysis of our cases and those reported in the literature shows that colistin is the most widely used therapeutic approach in the treatment of *A baumannii* infections in children.

In fact, polymyxin B and polymyxin E (colistin) are the most active agents in vitro, because of their potent activity to destroy bacterial cytoplasmic membranes and to cause leakage of cytoplasmic contents of certain MDR Gram-negative pathogens.

The use of polymyxins was abandoned in the 1960s because of their nephrotoxicity and neurotoxicity, but during the past few years the emergence of MDR Gram-negative bacilli has led to reconsider the use of such antibiotics. Recent studies show that current nephrotoxicity rates range up to 36%, whereas neurotoxicity is now uncommon, possibly because of different drug formulations, use of lower doses of antibiotics and careful ICU monitoring.⁵

Data on safety and efficacy of intravenous colistin administration in specific populations including neonates and children remain insufficient, because most of the studies were carried out with adult patients. Moreover, the few studies conducted in the paediatric population to evaluate colistin in infections caused by MDR Gram-negative bacteria mainly included patients with cystic fibrosis. However, a recent paediatric study, which excluded patients affected by cystic fibrosis, has showed good tolerability of intravenous colistin, even when given at relatively high dosage and for prolonged period in childhood.^{6 7}

Clinical reports of patients infected with *A baumannii* resistant to polymyxins are scarce. Nevertheless, the increasing use of polymyxins in critically ill patients may lead to the emergence of resistance.¹

Regarding polymyxin-based combination regimens, the best studied one involves rifampicin,⁸ which has shown synergistic in vitro activity against MDR *A baumannii* strains in most studies.

Among other possibilities, association with tigecycline is rarely described in the literature. Tigecycline is a new glycylcycline, which seems to have in vitro synergistic activity with colistin; as noted by various authors, colistin causes permeabilisation of the bacterial outer membrane, which could allow penetration of and activity by tigecycline.⁹ A recent study including 25 adult patients with VAP or bacteraemia treated with tigecycline in monotherapy or combined with different antimicrobials (imipenem or colistin) demonstrated clinical success in 84% of cases.¹⁰

Data related to the use of tigecycline in children are limited. Jaspan *et al*¹¹ have recently described the case of a 21-month-old girl affected by meningitis caused by MDR *Enterococcus faecium*, successfully treated with tigecycline. The dosing scheme used in this patient was 3 mg/kg/day intravenously, followed by a maintenance dosing of 2 mg/kg/day. However, no case-control randomised data are available in literature in relation to the use of combination therapy with tigecycline and colimicin in paediatric patients with MDR *A baumannii* infections.

Learning points

- *A baumannii* is a Gram-negative coccobacillus widespread in nature, which has emerged as an important nosocomial pathogen in recent years, especially in ICUs.
- Treatment of *A baumannii* infection has become difficult and only few therapeutic options are available.
- Although still off label in childhood, the combination therapy with colistin and tigecycline should be considered in MDR *A baumannii* severe infections unresponsive to carbapenems, taking into account their synergic activity in vitro. Case-control randomised studies are necessary to evaluate safety and efficacy of these antibiotics in the paediatric population.

Competing interests None.

Patient consent Obtained.

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