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CASE REPORT

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A case of pan-resistant *Burkholderia cepacia complex* bacteremic pneumonia, after lung transplantation treated with a targeted combination therapy

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Abstract

We describe a case of one patient with cystic fibrosis who developed a pan-resistant *Burkholderia cepacia complex* rapidly progressive bacteraemic pneunonia, following bilateral lung transplantation. The patient was treated with a targeted combination antibiotic therapy (meropenem plus ceftazidime/avibactam plus high doses of nebulized colistimethate sodium). Evolution of the disease was complicated by multiple organ system dysfunction. Finally, clinical improvement and microbiological cure was achieved.

KEYWORDS

bacteraemic pneumonia, lung transplantation, pan-resistant *Burkholderia Cepacia complex*

Burkholderia Cepacia complex (BCC) is recognized as a group of opportunistic pathogens in cystic fibrosis (CF) patients, usually associated with poor prognosis and patient-to-patient transmissibility. Despite recent advances that have been made in the understanding of the taxonomy and epidemiology of this group, respiratory infections of the respiratory tract with BCC organisms still have a considerable impact on morbidity and mortality in CF patient.[1] This bacterial infection has a major adverse impact on survival of CF patients after lung transplantation.[2] In the pre-transplant setting, BCC infection results in heterogeneous clinical outcomes, ranging from asymptomatic colonization to the most extreme manifestation, a fulminant respiratory failure, also known as cepacia syndrome.[3]

Burkholderia Cepacia complex is naturally resistant to different classes of antibiotics used in clinical practice and their pathogenicity is promoted by several virulence determinants.[4] These characteristics, together with the ability to adapt to environmental changes, make the treatment of BCC infections particularly challenging. It has been shown that during long-term colonization, BCC can undergo transcriptional reprogramming in response to different factors like, host immune response, antimicrobial therapy, nutrient availability, and oxygen limitation.

Herein, we describe the case of one patient with cystic fibrosis who developed a pan-drug resistant BCC rapidly progressive bacteremic pneumonia 7 months after a bilateral lung transplantation. The patient was treated with a targeted combination of two intravenous antimicrobials, meropenem plus ceftazidime/avibactam, and high doses of nebulized colistin with microbiological and clinical cure. Dissemination of this successful antimicrobial strategy can be of great aid for clinicians facing similar infections even in a less complicated scenario.

1 | CASE REPORT

A 27-year-old white man (body weight, 52 kg; height, 175 cm) was admitted to the hospital with a 48 h history of fever, malaise and breathlessness, 6 months after lung transplantation. He had been diagnosed with CF at the age of 7. His medical history included pancreatic insufficiency, bronchiectasis with sputum cultures showing BCC, multiresistant *P aeruginosa* that was repeatedly treated with inhaled ceftazidime based on in vitro antibiotic susceptibility test and *Scedosporium apiospermum* infection. He had also developed mild malnutrition, chronic rhinosinusitis, latent tuberculosis infection, subclinical hypothyroidism receiving thyroid hormone replacement

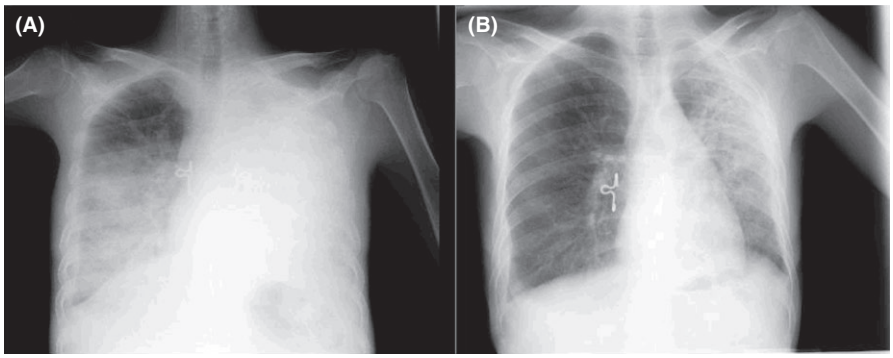

FIGURE 1 A, Chest X-ray taken ICU readmission day. B, Chest X-ray taken hospital discharge day

therapy, osteopenia with L_1 wedging, gastroesophageal reflux disease that was treated by a Nissen fundoplication and cor pulmonale with the need for oxygen therapy and intermittent non-invasive mechanical ventilation. He was referred for lung transplantation secondary to end-stage suppurative lung disease, and underwent sequential double lung transplantation 2 months later. For immunosuppression, he received tacrolimus 7 mg/12 h, mycophenolate mofetil 1.5 g/8 h and deflazacort 30 mg/d. Antibiotic and antiviral prophylaxis after hospital discharge included trimethoprim-sulfamethoxazole (160/800 mg), inhaled colistin (2 x 10^6 international units (IU)/12 h) and ganciclovir 900 mg/24 h.

Three months after his discharge from the hospital, he had fever (38°C), cough, and chest radiography showed a left lower lobe infiltrate. He was transferred to the pneumology ward and empirical treatment with meropenem and linezolid was started.

The patient presented with persistent fever and worsening of respiratory failure. Blood cultures, as well as cultures from the endotracheal aspirate, showed grew BCC. Treatment with Linezolid was stopped, meropenem 1 g/8 h was maintained and ceftazidime/avibactam (2/0.5 g/8 h) was added. A chest computer tomography (TC) showed persistent left lower lobe consolidation and right lower lobe ground glass infiltrate. The patient was transferred to the intensive care unit. On arrival he was hypoxic and with a severe respiratory failure, he was treated with high flow nasal cannula oxygen, over the next hours his respiratory status deteriorated, requiring intubation and mechanical ventilation. Serial chest X-rays showed worsening bilateral infiltrates as well as the original left-side consolidation. The cultures revealed a BCC which was resistant to several antibiotics, including meropenem (MIC ≥ 256 mg/L), ceftolozane/tazobactam (MIC = 128 mg/L), piperacillin/tazobactam (MIC ≥ 256 mg/L) and moxifloxacin (MIC ≥ 32 mg/L). Bacterial identification by Matrix Assisted Laser Desorption/Ionization–Time of Flight (MALDI–TOF) mass spectrometry yielded *B cepacia* complex and by sequencing the *recA* gene genomovar *cenocepacia* was obtained. The strain was susceptible only to ceftazidime/avibactam (MIC = 4 mg/L). All MIC values were determined using the gradient strip method. Treatment with meropenem was discontinued. Over the next week the chest X-ray and respiratory parameters improved. The control blood cultures and endotracheal aspirate obtained were negative. He was transferred to the pneumology ward after 10 days on ICU admission.

After a week he had a relapse with fever 39°C, respiratory failure and the chest X-ray showed extensive bilateral infiltrates (Figure 1A). From broth sputum and blood samples was recovered a BCC isolate which was multiresistant including meropenem (MIC ≥ 256 mg/L) and reduced susceptibility to ceftazidime/avibactam (MIC = 16 mg/L).

On the 20th day from admission, the patient was readmitted to the ICU with multiple organ dysfunction syndrome and septic shock. On arrival at the ICU he was intubated, placed on mechanical ventilation. He required high-dose vasopressor support and continuous renal replacement therapy (CRRT). We modified the immunosuppression regimen, mycophenolate mofetil was stopped and maintaining methylprednisolone 40 mg/12 h and tacrolimus titrated by blood levels. The patient was treated with ceftazidime/avibactam 2 g/8 h in extended infusion, and nebulized colistimethate sodium (CMS) 2 x 10^6 IU/8 h. In the ICU, we added meropenem 2 g/6 h in extended infusion and nebulized CMS was increased up to 5 x 10^6 IU/8 h using a vibrating plate nebulizer (Aerogen®Solo, Galway, Ireland). Meropenem (MIC in combination 0.5 mg/L) and ceftazidime/avibactam showed synergy by the gradient test method[5] (Table 1). Monitoring of intravenous antibiotics levels was carried out using high performance liquid chromatography from the Hospital Pharmacy Department. (Concentration at 50% of the dosing interval and trough levels for meropenem: 53.23 mg/L; 38.96 mg/L; and for ceftazidime/avibactam: 88.77 mg/L, 51.37 mg/L). Blood cultures drawn 72 h after the start of combined antibiotic treatment were negative.

In the following days, the clinical situation improved and on the 4th day ICU readmission, vasopressor support was stopped. On the 7th day renal function was recovered, and CRRT was stopped. A culture of bronchoalveolar lavage fluid on day 15 was negative. The patient was transferred to the ward 3 week after his second ICU admission. The combined antibiotic treatment was maintained for 26 days. The patient recovered successfully and he was discharged home 10 days later (Figure 1B).

2 | DISCUSSION

We report one case of successful treatment of pan-resitant BCC bacteraemic pneumonia in CF lung transplant recipients. Patients infected with BCC have higher mortality after transplantation.[1,2] Consequently, although the current guidelines[6] do not list BCC infection as an absolute contraindication to lung transplantation,

TABLE 1 Minimum inhibitory concentrations (MICs) and synergy test with gradient strip test

Antibiotic	MIC (mg/L)					
	Drug alone (Before T_{CZA})	Drug alone (After T_{CZA})	Drug + CT	FIX index with CT	Drug + CZA	FIX index with CZA
Tigecicline	>256	>256	16	0.19	4	0.35
Levofloxacine	>32	>32	>32	1.25	4	0.46
Moxifloxacine	>32	>32	>32	1.25	3	0.34
Fosfomycin	>1024	>1024	>1024	9.00	6	0.51
Colistin	>256	>256	>256	3.00	4	0.35
Meropenem	>32	>32	>32	1.25	0.5	0.06
Piperacilin/tazobactam	>256	>256	NT		NT	
Tobramycin	>32	>32	NT		NT	
Ceftolozane/tazobactam	128	128			1.5	0.14
Ceftazidime/avibactam	4	12				

CT: ceftolozane/Tazobactam; CZA: ceftazidime/avibactam; T_{CZA}: treatment with ceftazidime/tazobactam.
FIC index was calculated by (FIC of drug A) + (FIC of drug B), where FIC of drug A = (MIC of drug A in combination)÷(MIC of drug A alone), and FIC of drug B = (MIC of drug B in combination)÷(MIC of drug B alone). Synergism was defined as an FIC index of ≤0.5, additivity as an FIC index of >0.5 ≤ 1, indifference as an FIC index of >1 ≤ 2, and antagonism as an FIC index of >2.

"colonization with highly resistant or highly virulent bacteria" is included as a relative contraindication, thereby giving individual centers the ability to dictate practice. Moreover, high mortality has also been reported in a large cohort of non-CF patients with BCC bloodstream infections.[7]

To our knowledge, ours is the first reported case of pan-resistant BCC bacteraemic pneumonia. There is no current CLSI or EUCAST breakpoint for ceftazidime/avibactam and *B cepacia*, but the MIC value of 16 mg/L is over the PK/PD of non-species related breakpoint.[8] The clinical and microbiological success of this severe infection in a severely immunosuppressed patient infected with a pan-drug resistant pathogen deserves a speculative explanation, extrapolating the experience in other non-BCC bacteria. Nebulization permits the delivering of high concentrations of antibiotics in normal and infected lungs. Thus, Boisson et al[9] demonstrated that CMS and colistin concentrations in the epithelial lining fluid (ELF) following a single dose of 2 x 10^6 IU of CMS by aerosol delivery reached very high levels more than 1000 mg/L, exceeding 100 to 1000-fold plasma concentrations. This finding may explain that the pathogen resistant in vitro according to standard breakpoints could be eradicated by the high concentration achieved in lung tissue.

Papp-Wallace et al[10] found that when avibactam was combined with ceftazidime, susceptibility to ceftazidime in MDR and XDR clinical strains of Burkholderia spp isolated from CF respiratory specimens was restored. To the best of our knowledge, the synergism between ceftazidime/avibactam and meropenem against BCC has not been previously reported. However, this synergism has been described against other fastidious Gram-negative bacilli such as KPC-producing *Klebsiella pneumoniae*.[11]

Likewise, antibiotic concentration monitoring is of paramount importance because it offers the possibility to optimize the antimicrobial dosing. Importantly, both antimicrobials were used in extended infusions that optimize pathogen exposure to bactericidal concentrations of the β-lactams.[12] Although extended infusion of ceftazidime has been previously reported, only a case report has reported the use of extended-infusion ceftazidime/avibactam for a KPC-3-producing *Klebsiella pneumoniae* bacteraemia in a transplant patient.[13]

The optimization of antibiotic combinations and attenuation of immunosuppression for patients infected with BCC have been offered as means of improving survival for these patients following transplant. We applied this option and the patient was treated with a combination of intravenous ceftazidime/avibactam and high dose of meropenem optimizing the treatment by monitoring plasma antibiotics levels, in addition to high dose nebulized colistin. Our case evolved successfully after 26 days of antibiotic combination, achieving clinical and microbiological cure.

In conclusion, BCC infections represent a significant therapeutic challenge for clinicians, especially in the critical care setting. As in the case reported, clinicians must continue to assess each person patient individually, taking into account the in vitro antibiotic susceptibility data, previous clinical responses and their own experience. More studies are needed to assess the effectiveness of different antibiotic regimens and to improve the survival and quality of life of CF patients. For the management of this complicated and severe infection, a close interaction between the clinicians and the laboratories of Microbiology and Pharmacy is clearly necessary. Amongst the various in vitro methods of synergy assessment, time-kill assay, checkerboard assay and gradient strip-based methods are most commonly used. Checkerboard and gradient strip-based studies generally reported lower synergy rates than time-kill studies[14] when polymixins and carbapenems has been evaluated, but these studies

lack clinical validation. This case illustrates that the combination of high doses of nebulized colistin plus intravenous synergistic antibiotics with optimized dosing was effective in the management of a life-threatening infection caused by a pan-drug resistant bacteria in a severely immunosuppressed patient.

CONFLICT OF INTEREST

None.

AUTHOR'S CONTRIBUTION

MLCB and JGM conceived of the presented idea. All authors discussed the clinical case report and contributed to the final manuscript.

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