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Ceftobiprole in cystic fibrosis: a case series

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Background: Cystic fibrosis (CF) is an autosomal recessive disorder caused by mutations in the CF transmembrane conductance (*CFTR*) gene, resulting in the secretion of hyperviscous mucus. Infective exacerbations are a major determinant of morbidity and mortality in CF patients. These infections are clinically challenging, and antimicrobial treatment should effectively target the organisms and be delivered early to improve survival. Ceftobiprole is a fifth-generation cephalosporin antibiotic that is not indicated for the treatment of CF. However, due to its activity against common causes of infective exacerbations in CF such as *Staphylococcus aureus*, including MRSA, and *Pseudomonas aeruginosa* where resistance has not developed, it has utility for managing infective exacerbations.

Objectives: To describe the use of ceftobiprole in the treatment of infective exacerbations in CF.

Patients and methods: Ten patients with CF (age 24–63; six male and four female) were treated with ceftobiprole for infective exacerbations following discussion within the multi-disciplinary team. In most patients, ceftobiprole was given concomitantly with other antibiotics.

Results: All patients had positive sputum cultures for *S. aureus* (including nine MRSA), and seven patients had concomitant *P. aeruginosa* infection. Ceftobiprole treatment was associated with improved lung function, and markers of systemic inflammation decreased for most patients, with some variation. There was good tolerability in all but four patients.

Conclusions: Ceftobiprole presents a therapeutic option for susceptible infections in CF patients with limited treatment options. Its broad-spectrum coverage may help to reduce polypharmacy. However, further clinical studies are needed.

Introduction

Cystic fibrosis (CF) is a multi-systemic autosomal recessive disease caused by defective CF transmembrane conductance regulator (CFTR) protein expression due to *CFTR* gene mutation.[1,2] Pulmonary infective exacerbations are clinically important in patients with CF. They are polymicrobial, complex, challenging to treat,[3,4] and commonly caused by *Pseudomonas aeruginosa* (PsA), *Staphylococcus aureus*, *Haemophilus influenzae* and *Burkholderia cepacian*.[5] However, the epidemiology of infective exacerbations is changing, with increased incidence of MRSA, drug-resistant PsA and other Gram-negative non-fermenters such as *Stenotrophomonas maltophilia*.[6] Persistence of MRSA in the respiratory tract is associated with higher morbidity and mortality.[7]

The goal of antibiotic use for infective exacerbations is to control lung infections[1] and relieve symptoms to improve quality of life. Therapy should be optimized based on the severity and frequency of exacerbations, recent courses of anti-infectives, previously isolated pathogens and *in vitro* susceptibilities.[6] Inhaled azithromycin, tobramycin, aztreonam and levofloxacin are the main options, but other treatments may be used depending on exacerbation severity, local treatment guidelines[8] and individual sensitivities.[1]

MDR strains of PsA and drug hypersensitivity reactions have limited the effectiveness and number of antibiotics available to treat pulmonary exacerbations.[9] Furthermore, multiple-pathogen infections can require multiple antibiotics, adding to the polypharmacy burden in a highly medicated population and potentially increasing resistance. Suitable agents are needed to maximize the chance of bacterial eradication and reduce antibiotic pressure, alongside measures that reduce selection pressure such as antibiotic cycling.[10]

Ceftobiprole

Ceftobiprole (Zevtera®/Mabelio®) is a fifth-generation cephalosporin antibiotic with clinical efficacy against numerous Gram-positive and Gram-negative bacteria, including *S. aureus* (including MRSA), *Streptococcus pneumoniae* (including MDR *St. pneumoniae)*, *Escherichia coli* and *Klebsiella pneumoniae*.[11] It exerts bactericidal activity by binding penicillin-binding proteins in susceptible species.[11] In Gram-positive bacteria, including MRSA, ceftobiprole binds PBP2a, while in penicillin-intermediate and penicillin-resistant *St.* pneumoniae,[11] it binds PBP2b and PBP2x, respectively.

Ceftobiprole is approved for the treatment of hospital-acquired pneumonia (HAP) (excluding ventilator-associated pneumonia) and community-acquired pneumonia (CAP) in paediatric and adult patients.[11] It is administered as an intravenous (IV) infusion, three times daily.[11]

Although not indicated for CF treatment, ceftobiprole is effective against a broad spectrum of organisms, which impact morbidity and mortality in CF exacerbations.[5,7,11] Of particular relevance to our patient cohort is its activity against both *S. aureus* and PsA, where resistance has not developed. We therefore used ceftobiprole in a small cohort of patients with CF-related infective exacerbations in our hospital.

Patients and methods

This case series involved 10 patients with CF (age 24–63 years; six male and four female) treated for infective exacerbations with ceftobiprole (500 mg IV three times daily) at the Royal Brompton and Harefield Hospitals. Ceftobiprole was chosen as a therapeutic option for MRSA, especially where there were multiple organisms present, to reduce polypharmacy. The antibiotic treatment regimens for each patient are summarized in Table 1.

This study assessed clinical response to ceftobiprole using a composite of outcome measures commonly employed in CF research: improvement in forced expiratory volume in 1 s (FEV_1)/FEV_1% predicted, reduction in inflammatory markers (C-reactive protein [CRP] and WBC count), resolution of symptoms and ability to wean off IV antibiotics. For the purposes of this study, we determine treatment success as meeting any of the above outcome measures and the ability to discharge the patient, either on their usual antibiotic prophylactic regimen or requiring no treatment at all.

CRP (Figure 1), WBC (Figure 2) and FEV_1% predicted (Figure 3) measurements were taken before and after ceftobiprole was administered in most patients. Data from the first admission across all patients were assessed for normality using a Shapiro–Wilk test and analysed by two-tailed, paired *t*-test if appropriate.

As this was a service evaluation, ethical approval was not required, and the study was registered with the hospital's audit department.

Results

All 10 patients had sputum cultures positive for *S. aureus* (nine MRSA) and 7 had concomitant PsA infection. Overall, ceftobiprole administration was associated with a significant increase in patients' FEV_1% predicted of 9.05 ± 4.82 (±SD; 95% CI 4.60–13.51) (Figure 3, increase $P=0.0085$). A decrease in WBC (Figure 2, $P=0.0047$) was also observed, but no significant effect on CRP was found (Figure 1). Antibiotic resistance to ceftobiprole was not seen in this cohort. Good tolerability was observed in all but four patients. No patients had renal impairment requiring dose adjustments. Drug–drug interactions were not a feature of ceftobiprole in this study. Radiological data are not reported in this cohort due to limited availability. Though radiographs did not influence treatment decisions, they were used to provide evidence for diagnosis and disease resolution. Nine of the 10 patients were alive at the time of writing.

Patient 1

October 2016

An 18-year-old man with chronic MRSA infection and intermittent PsA infection was admitted with fever, worsening chest infection and a blocked portacath, resulting in several missed doses of IV at-home antibiotics (IV meropenem and colistimethate). This treatment was continued, with IV co-trimoxazole added to cover *Ste. maltophilia*. However, due to a lack of patient improvement, treatment was further altered to include IV ceftobiprole. Subsequently, CRP increased, WBC decreased and FEV_1% predicted improved from 30% to 35%, and the patient was later discharged.

May 2017

The patient was readmitted with an exacerbation, accompanied by right-sided chest pain, increased sputum production and dyspnoea, despite a prophylactic regimen. The FEV_1% predicted was 41%. Following admission, his treatment regimen was altered. However, the patient's temperature continued to spike, resulting in further alteration and the later addition of IV ceftobiprole. The patient's CRP and WBC decreased, and the patient was later discharged.

August 2017

The patient presented with sudden-onset severe pleuritic chest pain, exacerbated by coughing and deep inspiration, with an FEV_1% predicted of 27% on admission. Sputum production was unchanged, with no haemoptysis or fever. There was no change from his most recent chest X-ray report (July 2017), which showed severe bilateral bronchiectasis. Ceftobiprole was added to the treatment regimen. CRP and WBC fluctuated but decreased overall. Chest pain improved with analgesia (paracetamol and codeine). MRSA and carbapenem-resistant *Enterobacteriaceae* were isolated from patient swabs, and 5 days of MRSA eradication therapy was administered as per infection control protocols. He was later discharged with a predicted FEV_1% of 25%.

Patient 2

April 2017

A 38-year-old man with MRSA colonization/carriage history was admitted with a positive sputum culture for PsA on a background

Table 1. Summary of patient data

Patient	Details	Sputum culture	Date of admission	Antibiotic treatment	Ceftobiprole treatment		Notes and outcomes
					Start	Duration	
1	Male 24 years Alive	MRSA PsA	October 2016	• Admitted on IV colistimethate and meropenem, which were continued • IV co-trimoxazole added to cover *Ste. maltophilia* • IV meropenem replaced by IV ceftobiprole on Day 2	Day 2	14 days	• Discharged on Day 16 with IV aztreonam, oral co-amoxiclav and oral doxycycline
			May 2017	• Admitted on IV fosfomycin, IV colistimethate and oral linezolid • Oral linezolid stopped and IV colistimethate continued • IV fosfomycin changed to IV meropenem and IV teicoplanin added • After 2 days, oral linezolid reinstated and IV ceftobiprole added on Day 6 • IV teicoplanin stopped after 8 days	Day 6	12 days	• Discharged on Day 17 with IV colistimethate, IV meropenem and oral linezolid
			August 2017	• Started on IV teicoplanin and colistimethate • IV ceftobiprole added after 4 days	Day 4	18 days	• Discharged on Day 22 with IV teicoplanin, colistimethate and ceftazidime • Underwent lung transplant in October 2017
2	Male 39 years Deceased	MRSA PsA	April 2017	• Initially treated with doxycycline, then switched to co-trimoxazole due to tinnitus • IV ceftobiprole and nebulised aztreonam added on Day 5 • Antibiotics changed to IV fosfomycin and meropenem after 14 days	Day 5	14 days	• Discharged on Day 35 with IV aztreonam plus oral co-amoxiclav and doxycycline • Died 9 months later, unrelated to the infection
3	Male 29 years Alive	*S. aureus*	April 2018	• Started IV piperacillin/tazobactam, IV tobramycin and oral co-trimoxazole • Piperacillin/tazobactam and co-trimoxazole changed to IV ceftobiprole and tobramycin after 11 days	Day 12	6 days	• Discharged Day 18 with azithromycin, plus continuation of prophylactic antibiotics: alternating nebulized colistimethate and tobramycin
4	Male 40 years Alive	MRSA PsA	August 2017	• Started on IV teicoplanin, tobramycin and ceftobiprole alongside continuation of nebulized aztreonam • Teicoplanin and ceftobiprole stopped after 1 week, tobramycin continued • IV piperacillin/tazobactam and oral co-trimoxazole added	Day 2	7 days	• Discharged after 3 weeks
5	Female 25 years Alive	MRSA PsA	October 2018	• Received a course of IV ceftobiprole and tobramycin	Day 0	13 days	• Discharged on Day 13
			February 2019	• Received a course of IV ceftobiprole and tobramycin • Prophylactic azithromycin was temporarily stopped	Day 0	16 days	• Discharged on Day 16 with co-trimoxazole and fusidic acid
			May 2019	• Received a course of IV ceftobiprole and tobramycin	Day 0	13 days	• IV ondansetron added due to nausea • Discharged on Day 15
			July 2019	• Received a course of IV ceftobiprole and tobramycin	Day 0	9 days	• Discharged on Day 9
			September 2019	• Treatment at home with ciprofloxacin without improvement • IV ceftobiprole and tobramycin started on admission • Tobramycin changed to colistimethate on Day 8 due to patient trying to conceive	Day 0	13 days	• Discharged on Day 13 • Patient delivered a baby in 2021

Continued

Table 1. *Continued*

Patient	Details	Sputum culture	Date of admission	Antibiotic treatment	Ceftobiprole treatment		Notes and outcomes
					Start	Duration	
6	Female 41 years Alive	MRSA PsA	October 2017	• Received IV ceftobiprole and tobramycin for 5 days	Day 0	5 days	• Received a half-dose of lumacaftor/ivacaftor for 5 days • Discharged on Day 5 with oral co-trimoxazole
			March 2018	• Recently completed 2 wk course of home IV ceftazidime and tobramycin with oral linezolid • Received a course of IV ceftobiprole and tobramycin	Day 0	14 days	• Discharged on Day 14 with co-trimoxazole and fusidic acid
			October 2018	• Started on IV ceftobiprole and IV tobramycin • IV tobramycin was stopped as not tolerated	Day 0	13 days	• Discharged on Day 13
			June 2019	• Patient treated with IV ceftazidime and tobramycin at home • Tobramycin continued on admission • Ceftazidime changed to IV ceftobiprole	Day 0	12 days	• Discharged on Day 12
			December 2019	• Started on IV ceftobiprole and tobramycin	Day 0	14 days	• Discharged as a day case with IV ceftobiprole and tobramycin
			March 2020	• Started on IV ceftobiprole and tobramycin	Day 0	14 days	• Discharged as a day case with IV ceftobiprole and tobramycin
			June 2020	• Started on IV ceftobiprole and tobramycin at home • Patient developed a sore throat and rash shortly after first dose of ceftobiprole and tobramycin and so IV antibiotics stopped • Oral co-trimoxazole started instead	Day 3	1 day	• Daily fexofenadine and prednisolone due to possible allergic reaction to antibiotics co-administered • Discharged on Day 4
			March 2022	• Started a course of oral co-trimoxazole at home • Co-trimoxazole changed to oral minocycline and prednisolone after 10 days due to lack of improvement • Patient admitted 4 days later to start IV ceftobiprole and tobramycin • Patient once again developed a sore throat and rash after infusion • Ceftobiprole changed to IV teicoplanin, tobramycin continued	Day 0	1 day	• Discharged after 4 days with IV tobramycin and teicoplanin
7	Male 35 years Alive	MRSA	February 2019	• Admitted on IV tobramycin and oral doxycycline, IV ceftobiprole added • Patient developed skin lesions as a potential adverse reaction and so ceftobiprole and doxycycline stopped • Antibiotic treatment changed to vancomycin and linezolid	Day 0	2 days	• Discharged on Day 14 with meropenem and vancomycin
8	Male 47 years Alive	MRSA PsA	September 2020	• Admitted after community treatment with ciprofloxacin • Received course of IV ceftobiprole, which was associated with worsening chronic pancytopenia	Day 0	7 days	• Discharged on Day 11 with nebulised aztreonam
9	Female 63 years Alive	MRSA	January 2021	• Admitted on ciprofloxacin and flucloxacillin • Started on IV ceftazidime and IV tobramycin • Switched to IV ceftobiprole when sputum grew MRSA and full 14 day course was well tolerated	Day 2	14 days	• Also trialled on 7% hypertonic saline which was not tolerated • Discharged on Day 28 with oral doxycycline

10	Female 57 years Alive	MRSA PsA	June 2021	• Received course of IV ceftobiprole and colistimethate	Day 0	10 days	• Discharged on Day 10 with oral ciprofloxacin • Symptoms worsened after course was completed. A dose of ciprofloxacin was given and then IV ceftobiprole re-commenced • Patient had severe reaction to second dose of new ceftobiprole course Ceftobiprole stopped and patient treated with IV fluids, chlorphenamine and hydrocortisone • Treatment switched to oral linezolid and meropenem with IV tobramycin

of a viral and super-added bacterial infection. His initial treatment was altered with no improvement, and IV ceftobiprole and nebulized aztreonam were later added. The dosage of his maintenance corticosteroid (prednisolone) was transiently increased, and tranexamic acid was started for recurrent small haemoptysis. The patient gradually improved but felt increasingly tired and breathless, and treatment was subsequently changed with good response. The FEV_1% predicted increased from 30% on admission to 39% at discharge.

Patient 3

April 2018

A 24-year-old man was admitted with nausea, abdominal pain and increasing dyspnoea. His prophylactic antibiotics were alternating nebulized colistimethate and tobramycin. This patient had a history of positive MRSA sputum culture, PsA infection (although he has been culture negative since November 2015) and allergies to both meropenem and flucloxacillin. On admission, he was commenced on an antibiotic treatment with a sputum culture growing *S. aureus*. However, he showed no improvement, resulting in treatment alteration to IV ceftobiprole and tobramycin. His CRP and WBC were not raised, but FEV_1% predicted improved from 32% at baseline to 50% upon discharge. At follow-up, the patient had intermittent *S. aureus* infection.

Patient 4

August 2017

A 34-year-old man was admitted with a productive cough, tiredness, fever and left-sided chest discomfort. He was ceftazidime intolerant, with a history of recurrent pneumothoraces, chronic PsA and MRSA infection, *Mycobacterium avium* complex (although recent cultures were negative) and required ambulatory oxygen. The patient started IV teicoplanin, tobramycin and ceftobiprole alongside the continuation of nebulized aztreonam. Initially, CRP and WBC reduced, but after 1 week, CRP started to increase, his chest still felt tight and his oxygen requirement remained high. His regimen was altered, including the stopping of ceftobiprole and addition of other agents, with good effect. The FEV_1% predicted increased from 21% at baseline to 32% on Day 15, and the patient was later discharged.

Patient 5

October 2018

A 21-year-old woman was admitted with a background of chronic MRSA and PsA infection. She had a 1 month history of increased cough, chest tightness, sputum production and weight loss. Her FEV_1% predicted at this time was 45%. IV tobramycin and ceftobiprole were commenced with positive resolution of her raised CRP and WBC. The FEV_1% predicted was 48% at discharge.

February 2019

She was readmitted with a 5 day history of fever, sweating, increased cough, sputum production and two episodes of haemoptysis (baseline FEV_1% predicted was 48%). She was immediately started on IV ceftobiprole and tobramycin, leading to a decrease

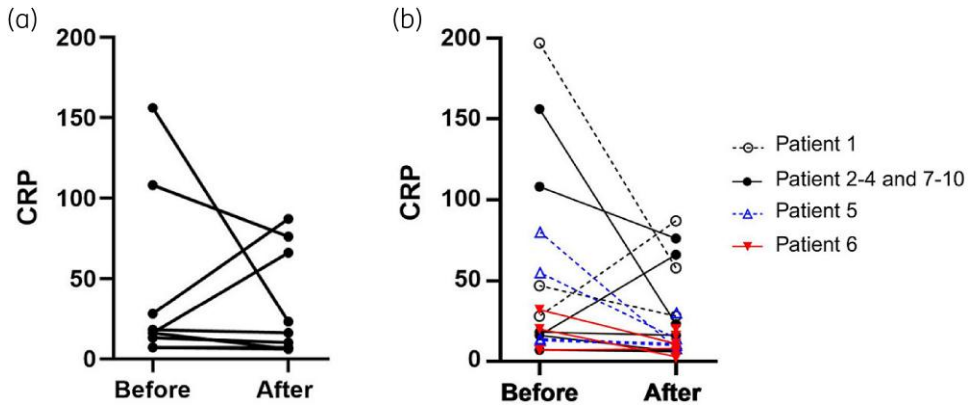

Figure 1. CRP serum concentration before and after dosing with ceftobiprole for all patients combined at first admission (a) and across all admissions (b). Before measurements were taken up to 3 days before the start of ceftobiprole administration, and After measurements between 2 and 4 days after. Note: In most patients, ceftobiprole was given concomitantly with other antibiotics (see Table 1).

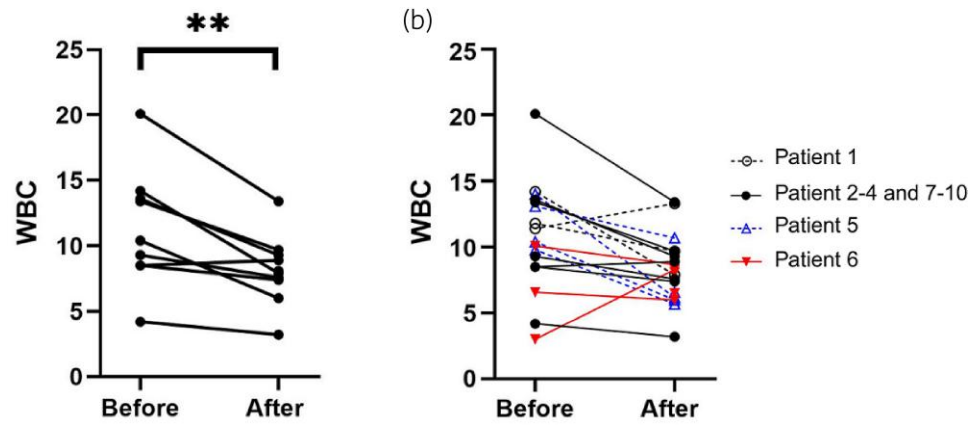

Figure 2. White blood cell count (WBC) before and after dosing with ceftobiprole for all patients combined at first admission (a) and across all admissions (b). Before measurements were taken up to 3 days before the start of ceftobiprole administration, and After measurements between 2 and 4 days after. Data in (a) were analysed by two-tailed, paired *t*-test, $^{**}P < 0.01$. Note: In most patients, ceftobiprole was given concomitantly with other antibiotics (see Table 1).

in CRP and WBC, although her FEV_1% predicted did not change substantially, and she was later discharged.

May 2019

The patient was readmitted after a small haemoptysis with increasing sputum production and 92% oxygen saturation. Chest X-ray showed increased peribronchial thickening compared with February 2019. IV tobramycin and ceftobiprole were commenced and well tolerated, with rapid symptom improvement and decreased CRP and WBC. During the latter stages of treatment, she complained of increasing nausea without vomiting, which resolved with IV ondansetron. The FEV_1% predicted was 48% at admission and 52% at discharge.

July 2019

With decreased FEV_1% predicted (recorded as 37%), increasing sputum, chest pain and fevers, the patient was readmitted. Treatment with IV ceftobiprole and tobramycin resulted in good resolution of infective markers and improvement in symptoms. At discharge, 9 days after admission, the FEV_1% predicted had improved to 48%.

September 2019

The patient was readmitted with borderline hypoxia, wheezing, breathlessness, night fevers, intermittent haemoptysis and weight loss. Showing no improvement despite home treatment, she started IV ceftobiprole and tobramycin with good response and a decrease in CRP and WBC. She was later discharged.

Patient 6

October 2017

A 36-year-old woman with a history of multiple antibiotic allergies was admitted with chronic infection with MRSA and PsA (baseline FEV1% predicted was 35%). Upon admission, she was commenced on a 5 day course of IV ceftobiprole and tobramycin.

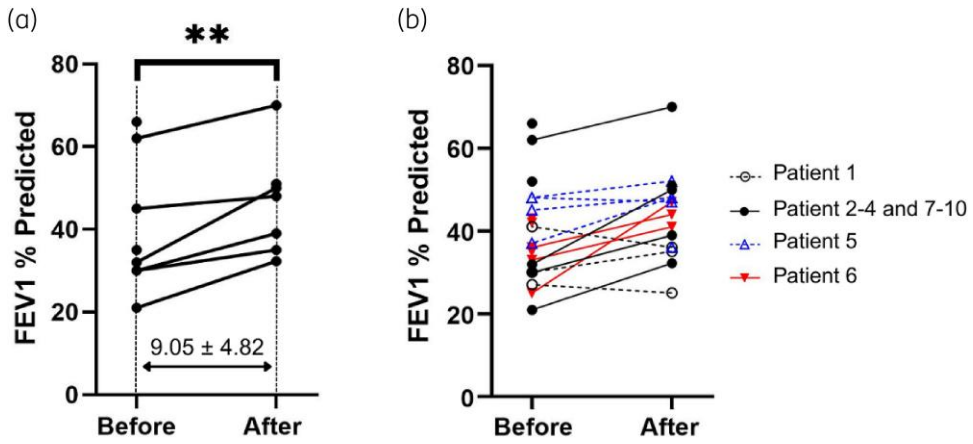

Figure 3. Forced expiratory volume in 1 s (FEV_1) % predicted before and after dosing with ceftobiprole for all patients combined at first admission (a) and across all admissions (b). Measurements were taken ~2 weeks before and after the start of ceftobiprole administration, with some variation. Data in (a) were analysed by two-tailed, paired *t*-test, $^{**}P < 0.01$. Mean difference between groups: 9.05 ± 4.82 (±SD), 95% CI 4.60–13.51. Note: In most patients, ceftobiprole was given concomitantly with other antibiotics (see Table 1).

Overnight, she developed swollen wrists and small joints, which settled spontaneously. She was concurrently on lumacaftor/ivacaftor, which was discontinued after 5 days due to dyspnoea requiring nebulized salbutamol, persistent chest tightness, decrease in saturations and a 10% decline in pulmonary function. The patient was subsequently discharged.

March 2018

She was readmitted with a cough, lethargy, hot sweats and increased sputum production although she had completed a home antibiotic regimen (a 2 week course of IV ceftazidime, tobramycin and oral linezolid). A chest X-ray showed new opacities, likely representing active inflammatory changes. She was started on a 14 day course of IV ceftobiprole, with added IV tobramycin the following day. There was good response; her CRP and WBC decreased and the FEV_1% predicted improved from 25% to 47% and she was later discharged.

October 2018

The patient was readmitted, with FEV_1% predicted declining to 35%. Her chronic MRSA infection persisted, and PsA was re-isolated. She was commenced on IV ceftobiprole/tobramycin and was later discharged.

June 2019

The patient was readmitted with an infective exacerbation and was switched to IV ceftobiprole/tobramycin. This was well tolerated, and the FEV_1% predicted increased from 33% at admission to 41% at discharge.

December 2019

The patient was readmitted with coughing fits, increased sputum production and tiredness. Sputum from 11 days prior grew MRSA. She was discharged the same day with IV ceftobiprole and tobramycin. The FEV_1% predicted increased from 36% at admission to 44% by the end of treatment.

March 2020

The patient was readmitted for an infective exacerbation. Due to social distancing measures in place during the COVID-19 pandemic, she was discharged the same day with IV ceftobiprole and tobramycin for home administration. Over the next 2 days, she experienced facial redness and itchiness, which resolved and was deemed unrelated to the antibiotic.

June 2020

Due to worsening lung function and chest tightness, the patient began IV tobramycin and ceftobiprole at home. Within hours of the first dose, she developed facial redness, a chest and back rash, throat itchiness and painful swallowing, though her breathing remained unaffected. Her regimen was altered to co-trimoxazole. She further developed a first episode of haemoptysis, so she started tranexamic acid and attended the outpatient clinic.

March 2022

The patient presented with deteriorating lung function, fever and headaches indicating infection, with FEV_1% predicted declining from 53% to 44%. She began a course of co-trimoxazole at home, but due to a lack of improvement, she was readmitted to hospital and started on IV ceftobiprole and tobramycin. Despite prior reported reactions, allergy testing ruled out a true ceftobiprole allergy. However, after re-challenge with ceftobiprole, the patient developed a rash and sore throat overnight, and her oxygen saturation dropped to 95%. Symptoms commenced 30–90 min after the infusion began and ceased within 1 h of infusion completion. Her treatment was switched to IV tobramycin and teicoplanin, and she was discharged on Day 4 to complete the treatment course at home.

Patient 7

February 2019

A 31-year-old man, with chronic MRSA infection, was admitted due to an infective exacerbation with a productive cough and

chest tightness. Ceftobiprole along with doxycycline was given for MRSA coverage but was discontinued after he developed depigmented lesions on his chest, arms and hands, consistent with previous severe drug reactions. Following treatment adjustment and clinical improvement, he was discharged.

Patient 8

September 2020

A 44-year-old man was admitted with dyspnoea, chest tightness, fatigue and congestion. He had chronic PsA and MRSA infection, CF-related diabetes, gastro-oesophageal reflux disease (GORD), CF-related liver disease with cirrhosis and dilated cardiomyopathy. His initial community treatment was ineffective, and upon admission, he was started on IV ceftobiprole for 7 days. Chronic pancytopenia observed at admission was thought to be worsened by ceftobiprole, and when ceftobiprole was stopped, an improvement in blood counts was seen. The patient was subsequently discharged with a suppressive therapy regimen.

Patient 9

January 2021

A 61-year-old woman was admitted with a history of MRSA and *S. aureus* resistant to erythromycin and penicillin isolated from a sputum culture 10 months prior. Her previous treatment was ineffective and was adjusted upon admission. Based on a new MRSA sputum culture, she was later started on 14 days of IV ceftobiprole.

The treatment was well tolerated, but she developed respiratory symptoms 1 day after completing the course and received a dose of ciprofloxacin. She then developed temperatures and consequently re-commenced IV ceftobiprole, but after the second dose, she became sweaty, tachypnoeic and tachycardic, with decreased oxygen saturation. She also developed an erythematous petechial and blanching rash. Ceftobiprole infusion was stopped, the reaction was managed and antibiotic treatment was subsequently switched. Following improvement, the patient was discharged.

Patient 10

June 2021

The patient was admitted with symptoms of fatigue, increased cough, progressive dyspnoea on exertion and headache, with pleuritic pain in the right shoulder, with wheeze and tight chest. Her most recent sputum sample (March 2021) tested positive for MRSA, with chronically isolated PsA. Her treatment included 10 days of IV ceftobiprole, and upon discharge, she was clinically stable, with an improvement in FEV_1% predicted from 62% to 70%.

Discussion

To the best of our knowledge, this is the first case series describing ceftobiprole use to manage infective exacerbations due to PsA and MRSA in CF patients. Ceftobiprole is licensed to treat pneumonia[11] and achieves good concentrations in the lungs.[12]

Good tolerability was observed in over half of our patients (6/10), though the proportion who experienced possible treatment-related adverse events was relatively high (4/10). In a Phase III randomized clinical trial performed in patients with HAP, 24.9%[13] experienced treatment-related adverse events with ceftobiprole, while another study in patients with CAP reported an incidence of 36.3%.[14] Given our small patient cohort, combined with the complex medical history typical of CF patients, the observed adverse events rate may reflect underlying patient factors rather than a ceftobiprole-specific safety concern. Ceftobiprole could be a viable treatment option in these patients, but further studies may be warranted to characterize its safety profile in this population better.

Ceftobiprole treatment was associated with an improvement in lung function in this study, as shown by an increase in FEV_1% predicted. Although treatment was associated with a decrease in WBC, there was no consistent effect of ceftobiprole treatment on CRP. Monitoring treatment response in CF patients can be challenging. However, elevated CRP levels 5 days after antibiotic treatment do not necessarily indicate treatment failure.[15] While CRP and other systemic inflammatory markers may be more sensitive and could correlate with important outcomes like lung function[16] and predict exacerbation recurrence,[17] other factors, including clinical signs, lung function, radiology and oxygen saturations, hold significance.

This study highlights the challenges in managing CF-related infective exacerbations. Eradication of organisms is difficult, and there is continuous dependence on antibiotics. Therefore, antimicrobial stewardship procedures should be implemented as good clinical practice, particularly for complex CF patients experiencing repeat infective exacerbations.

Ceftobiprole administrations were given as at-home IV therapy to one patient on multiple occasions, which would benefit from further investigation. With the wider acceptance of patients with chronic disease being taught to self-administer antibiotics, this antibiotic option, pending sensitivities, widens the repertoire of antibiotics available to manage CF-related infections, potentially reducing polypharmacy.

Limitations

The small sample size in this study means that more real-world experience is needed to further examine the clinical effectiveness of ceftobiprole in CF patients. Ceftobiprole was administered concomitantly with other antibiotics in all cases, making it challenging to definitively attribute the observed efficacy solely to ceftobiprole.

Conclusions

In this study, we suggest that ceftobiprole presents a therapeutic option for individuals with CF, particularly where pathogen susceptibility is demonstrated, in a setting where treatment options are severely limited.

One potential advantage is its broad-spectrum coverage, with activity against pathogens commonly observed colonizing the airways of CF patients. This may help reduce polypharmacy in polymicrobial infections, thereby promoting antimicrobial stewardship and positioning it as a therapeutic option for such infections. However, our study was not designed to confirm this benefit, and future prospective clinical studies will be needed to evaluate this further.

Additionally, a key challenge in clinical practice is physician confidence in using a single antimicrobial, particularly in critically ill patients. Despite known susceptibility as per the manufacturer's summary of product characteristics (SmPC),[11] our findings indicate a culture where clinicians are hesitant to use it in isolation, likely due to concerns about treatment failure in this vulnerable population. This highlights an important barrier to antimicrobial optimization that warrants further investigation.

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Transparency declarations

None declared.

Author contributions

S.C. was responsible for the conception and design of the study. L.N. was responsible for the acquisition of data, its subsequent analysis, and the drafting and revision of the article. N.R. was responsible for data acquisition. All three authors approved the final manuscript.

References

1 Rafeeq MM, Murad HAS. Cystic fibrosis: current therapeutic targets and future approaches. *J Transl Med* 2017; **15**: 84. https://doi.org/10.1186/s12967-017-1193-9

2 Radlovic N. Cystic fibrosis. *Srp Arh Celok Lek* 2012; **140**: 244–9. https://doi.org/10.2298/SARH1204244R

3 Lord R, Jones AM, Horsley A. Antibiotic treatment for *Burkholderia cepacia* complex in people with cystic fibrosis experiencing a pulmonary exacerbation. *Cochrane Database Syst Rev* 2020; **4**: CD009529. https://doi.org/10.1002/14651858.CD009529.pub4

4 Filkins LM, O'Toole GA. Cystic fibrosis lung infections: polymicrobial, complex, and hard to treat. *PLoS Pathog* 2015; **11**: e1005258. https://doi.org/10.1371/journal.ppat.1005258

5 Leitch A, Rodgers H. Cystic fibrosis. *J R Coll Physicians Edinb* 2013; **43**: 144–50. https://doi.org/10.4997/JRCPE.2013.212

6 Parkins MD, Elborn JS. Newer antibacterial agents and their potential role in cystic fibrosis pulmonary exacerbation management. *J Antimicrob Chemother* 2010; **65**: 1853–61. https://doi.org/10.1093/jac/dkq245

7 Fusco NM, Toussaint KA, Prescott WA. Antibiotic management of methicillin-resistant *Staphylococcus aureus* –associated acute pulmonary exacerbations in cystic fibrosis. *Annals of Pharmacotherapy* 2015; **49**: 458–68. https://doi.org/10.1177/1060028014567526

8 Brompton local antimicrobials guideline: Royal Brompton & Harefield NHS Foundation Trust Antimicrobial Prescribing guide 2019.

9 Spoletini G, Kennedy M, Flint L *et al.* Intravenous fosfomycin for pulmonary exacerbation of cystic fibrosis: real life experience of a large adult CF centre. *Pulm Pharmacol Ther* 2018; **50**: 82–7. https://doi.org/10.1016/j.pupt.2018.04.007

10 Abel zur Wiesch P, Kouyos R, Abel S *et al.* Cycling empirical antibiotic therapy in hospitals: meta-analysis and models. *PLoS Pathog* 2014; **10**: e1004225. https://doi.org/10.1371/journal.ppat.1004225

11 ADVANZ PHARMA. Summary of Product Characteristics: Zevtera 500 mg Powder for Concentrate for Solution for Infusion. 2022. https://www.medicines.org.uk/emc/product/9164/smpc.

12 Giacobbe DR, De Rosa FG, Del Bono V *et al.* Ceftobiprole: drug evaluation and place in therapy. *Expert Rev Anti Infect Ther* 2019; **17**: 689–98. https://doi.org/10.1080/14787210.2019.1667229

13 Awad SS, Rodriguez AH, Chuang Y *et al.* A phase 3 randomized double-blind comparison of ceftobiprole medocaril versus ceftazidime plus linezolid for the treatment of hospital-acquired pneumonia. *Clin Infect Dis* 2014; **59**: 51–61. https://doi.org/10.1093/cid/ciu219

14 Nicholson SC, Welte T, File TM Jr *et al.* A randomised, double-blind trial comparing ceftobiprole medocaril with ceftriaxone with or without linezolid for the treatment of patients with community-acquired pneumonia requiring hospitalisation. *Int J Antimicrob Agents* 2012; **39**: 240–6. https://doi.org/10.1016/j.ijantimicag.2011.11.005

15 Sharma A, Kirkpatrick G, Chen V *et al.* Clinical utility of C-reactive protein to predict treatment response during cystic fibrosis pulmonary exacerbations. *PLoS One* 2017; **12**: e0171229. https://doi.org/10.1371/journal.pone.0171229

16 Muhlebach MS, Clancy J, Heltshe SL *et al.* Biomarkers for cystic fibrosis drug development. *J Cyst Fibros* 2016; **15**: 714–23. https://doi.org/10.1016/j.jcf.2016.10.009

17 Girón-Moreno RM, Justicia JL, Yamamoto S *et al.* Role of C-reactive protein as a biomarker for prediction of the severity of pulmonary exacerbations in patients with cystic fibrosis. *BMC Pulm Med* 2014; **14**: 150. https://doi.org/10.1186/1471-2466-14-150