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BRIEF REPORT

Eradicating Pulmonary *Mycobacterium abscessus*: The Promise of Dual β-Lactam Therapy

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Macrolide resistance has rendered the treatment of *Mycobacterium abscessus* extremely difficult and is fueling a crisis. Recently, there has been dramatically increased incidence of infections by *M abscessus*. Select dual β-lactam combinations have shown promising in vitro results. Herein, we present a patient whose *M abscessus* infection cured using dual β-lactams as part of multidrug regimen.

Keywords. *Mycobacterium abscessus*; β-lactams; peptidoglycans; dual β-lactams; resistant mycobacteria; macrolide resistance.

Mycobacterium abscessus infection is notoriously difficult to treat, and treatment failure is not uncommon despite the use of multidrug regimens. Even with a combination of antibiotics, treatment may take several months, and relapse rates remain high. *M abscessus* pulmonary disease caused by macrolide-resistant strains, including subspecies *abscessus* and acquired mutations in the *rrl* target in other subspecies, poses a significant challenge for clinicians owing to poor culture conversion rates compared with macrolide-susceptible *M abscessus* subsp *massiliense* [1]. Dual β-lactam therapy, targeting multiple cell wall enzymes through differential binding, has shown promise as a highly effective strategy according to our laboratory data [2]. Here, we present a case of treatment-experienced pulmonary *M abscessus* infection that was treated with induction ceftaroline-imipenem as part of a multidrug regimen, and we recount the challenges faced during the treatment of this infection.

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CASE REPORT

A 39-year-old patient with history of successfully treated pulmonary tuberculosis 15 years earlier was found to have nodular opacities and bronchiectasis at screening chest radiography. Subsequent workup revealed macrolide-susceptible *M abscessus* subsp *massiliense* in sputum cultures. At the time of this diagnosis, the patient was receiving care was at a different medical institution. He was noted to be asymptomatic, and no treatment was offered. However, after 2 years of clinical follow-up, a cough developed. Chest computed tomography revealed radiographic progression (Supplementary Figure 1), and sputum cultures continued to exhibit growth of *M abscessus* subsp *massiliense*. The patient was then placed on treatment with daily intravenous amikacin, imipenem, and oral azithromycin for 2 months, followed by inhaled amikacin and oral azithromycin for 9 months.

According to records from the outside institution, the patient's condition initially improved and culture conversion was achieved after 5 months of therapy, but his infection relapsed; cultures showed growth of *M abscessus* subsp *massiliense* with high-level macrolide resistance due to mutation in the ribosomal *rrl* gene (per molecular assay performed at National Jewish Health Laboratory in Denver, Colorado), with an azithromycin minimum inhibitory concentration (MIC) of >256 μg/mL. Further phenotypic drug-susceptibility testing revealed the following MICs for amikacin, clofazimine, imipenem, linezolid, minocycline, and tigecycline, respectively: milliliter: ≤8, ≤0.5, >16, >16, >8, and 1 μg/mL. At this time, the patient was referred to our institution for evaluation of drug-resistant *M abscessus* infection.

We initiated a regimen that included oral clofazimine (100 mg once daily), intravenous amikacin (20 mg/kg 3 times weekly), imipenem (1 g twice daily), and tigecycline (50 mg twice daily). Tigecycline was discontinued after a few days owing to severe nausea. Given the limited therapeutic options, in vitro dual β-lactam combination testing was performed, indicating that imipenem and ceftaroline together were highly synergistic (Supplementary Table 1). Therefore, ceftaroline (600 mg 3 times daily) was added to the patient's treatment regimen, which already included clofazimine, imipenem, and intravenous amikacin (with dosing based on normal creatinine clearance). The patient received ceftaroline-imipenem for 2 months before the combination was stopped because of elevated liver enzyme levels and replaced by oral omadacycline (300 mg once daily).

Sputum culture conversion was achieved 161 days after initiation of antibiotics, 1 month after completion of combination treatment with ceftaroline and imipenem (Figure 1). After

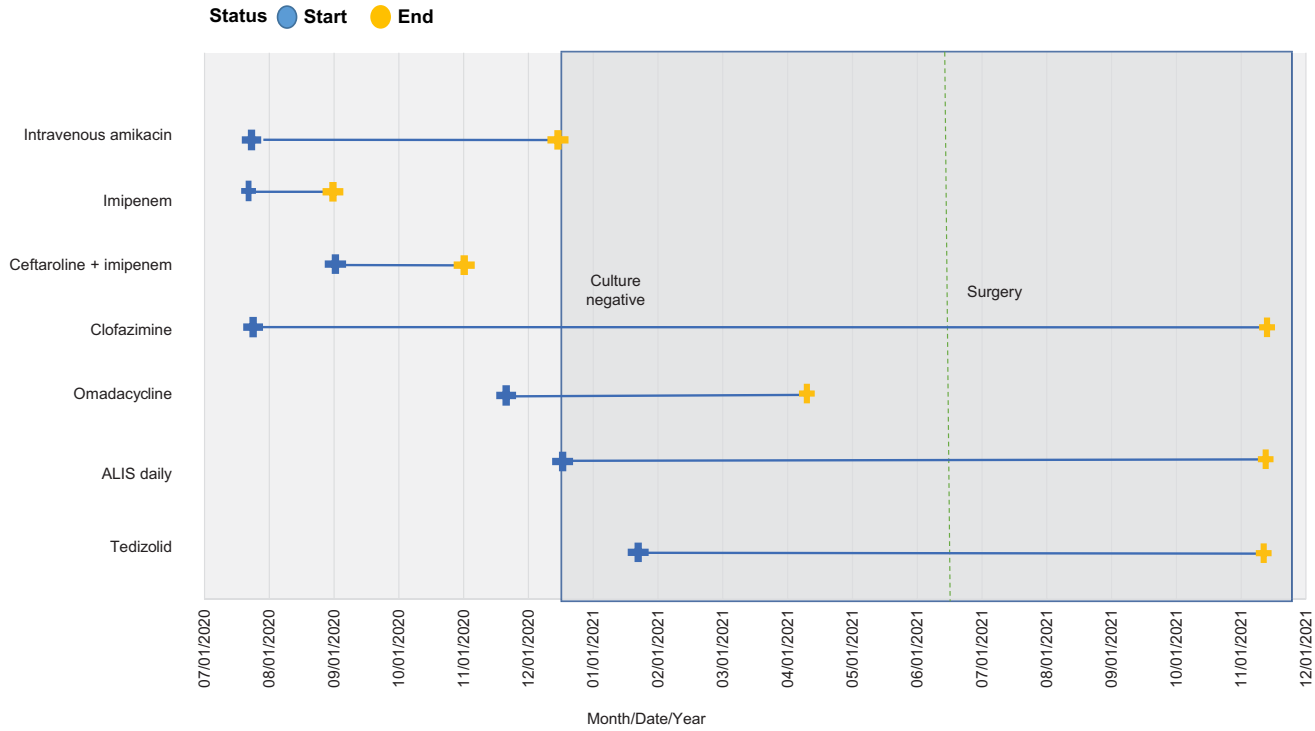

Figure 1. Temporal association between the administration of antimicrobial agents and culture conversion, Abbreviation: ALIS, amikacin liposome inhalation suspension.

culture conversion, the patient's treatment plan was modified to include inhaled liposomal amikacin instead of intravenous amikacin, oral clofazimine and omadacycline were continued, and tedizolid was added in an attempt to enhance medical therapy in preparation for planned resection of the diseased parts of the lung. Omadacycline course was complicated by nausea, vomiting, and a rise in liver enzyme levels and was stopped after 5 months. Six months after sputum culture conversion, the patient underwent lingulectomy, followed by right middle lobe resection 3 months later. All cultures obtained during surgery and histopathological examinations were negative for evidence *M abscessus* infection. Consequently, the consolidation regimen of clofazimine, tedizolid, and inhaled liposomal amikacin was discontinued 2 months later, after the surgical culture results became available.

At the most recent follow-up, 1 year and 7 months after the patient stopped antibiotics, there was no evidence of recurrence. The patient has diligently followed a twice-daily airway clearance regimen consisting of inhaled hypertonic saline throughout the antibiotic course, which is being continued indefinitely as part of long-term bronchiectasis management. In addition, owing to the recurrent nature of *M abscessus* infection, the patient underwent evaluation by a gastroenterologist, which was negative for gastroesophageal reflux disease or other gastrointestinal dysmotility.

Written informed consent was not obtained from the patient because our report involved only presentation of anonymized data that did not reveal his identity. Therefore, the patient's privacy and confidentiality were protected, and no potential harm or risk was posed to him.

DISCUSSION

Mycobacterium abscessus has been genomically characterized into 3 subspecies: *abscessus*, *bolletii*, and *massiliense* [3]. Treatment of *M abscessus* infection presents significant challenges and is considered a Sisyphean task for many infectious disease clinicians. This is primarily owing to its innate resistance to many commonly used antimicrobials [3] and its ability to survive in various environments, including within biofilms [4]. The therapeutic challenge faced by clinicians is further heightened by the emergence of multidrug-resistant strains that necessitate the use of multiple antimicrobials in combination and carry the potential for significant toxic effects [5]. In recent years, several laboratories have investigated the in vitro activity of dual β-lactam combinations as a potential treatment option for *M abscessus* infection [6–11]. These studies demonstrated that various combinations of β-lactam antibiotics, such as the combination of a carbapenem and cephalosporin or aminopenicillin, with or without β-lactamase inhibitors, may be clinically efficacious. We describe the first case documenting the clinical use and outcome of novel ceftaroline-imipenem combination therapy guided by in vitro synergy testing, as part of a multidrug regimen for the treatment of *M abscessus* lung infection.

β-Lactams have long been recognized to have activity against *M abscessus*, and imipenem or cefoxitin are recommended in

the current American Thoracic Society/Infectious Diseases Society of America treatment guidelines [12]. However, *M abscessus* harbors a β-lactamase (Bla_{Mab}), which may limit the efficacy of β-lactams. More recently, ceftaroline-imipenem activity was investigated in vitro [6] and found to be highly synergistic without the need for *M abscessus* (Bla_{Mab}) inhibition. This held true for a collection of *M abscessus* subsp *abscessus* clinical isolates, in which a fixed concentration of ceftaroline added to imipenem significantly lowered MICs. A potential explanation is offered by the concept of "target redundancy," which implies that differential inhibition of essential penicillin-binding proteins and L,D transpeptidases (classic and nonclassic enzymes, respectively, that catalyze transpeptidation in cell wall synthesis) by the 2 agents would result in a lower MIC than with a single agent.

This case highlights the multiple challenges associated with management of *M abscessus* infections. Our patient came into our care with recurrent, drug-resistant *M abscessus* infection associated with high-level macrolide resistance, induced by prior azithromycin use, which is known to be linked to a very poor treatment outcome [13]. Therapeutic options were greatly limited by the susceptibility profile of the isolate and were made more challenging by gastrointestinal intolerance to multiple agents (tigecycline, omadacycline, and dual β-lactams). Therapy required frequent monitoring and multiple changes in the regimen toward eventual clearance of sputum cultures.

Culture conversion occurred shortly after completion of 8 weeks of dual β-lactam therapy, suggesting that this novel, synergistic combination helped achieve clearance of infection as part of a multidrug regimen. Based on our case, we certainly cannot attribute culture clearance to dual β-lactam therapy alone, but we can speak to the viability of this approach in the management of similar patients who have limited therapeutic options owing to drug resistance and medication intolerance. Our patient did undergo eventual surgical resection, but it should be noted that clearance of cultures was achieved and sustained during the 6 months before surgery with multiple antimicrobials and diligent airway clearance therapy. Surgical resection of the diseased lung allowed us to eventually stop the antibiotics and has helped prevent recurrence of infection in our patient.

In conclusion, successful clearance of sputum cultures was achieved through the administration of a multidrug regimen. The combination of ceftaroline and imipenem, along with other agents, played a significant role in eliminating the infection. However, it is important to acknowledge that the success of achieving culture conversion cannot be solely attributed to dual β-lactam therapy (ceftaroline and imipenem). The synergistic interplay of amikacin, ceftaroline-imipenem, omadacycline, and clofazimine likely contributed to the successful outcome. Nevertheless, it is worth noting that the regimen of thrice-daily ceftaroline was associated with elevated hepatic enzyme levels. Clinical experience from National Jewish Health in Denver suggest that successful outcomes may be achieved with a twice-daily dosing schedule for ceftaroline [1].

The use of dual β-lactams shows promise as a part of a multidrug regimen for the treatment of *M abscessus* infection. However, further data are required to determine the definitive role of dual β-lactams such as ceftaroline-imipenem. Surgical resection of the diseased parts of the lung offers the prospect of long-term cure. Our approach of achieving culture clearance with optimal medical therapy before surgery, aimed to minimize the infectious burden in tissue, reducing the risk of complications after resection.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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Potential conflicts of interest. All authors: No reported conflicts.

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