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Case Report

New Delhi Metallo-β-Lactamase in Fresh Lung Transplant

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Abstract

We have presented, to the best of our knowledge, the first reported case of NDM and KPC-producing carbapenem-resistant *Enterobacter cloacae* correlated with life-threatening pneumonia and subsequent treatment. The pathogen was isolated from the lungs of a fresh bilateral lung transplant patient. Successful clearing of the BAL culture and clinical cure was achieved by combination therapy of meropenem/vaborbactam, levofloxacin, and nebulized amikacin/colistin.

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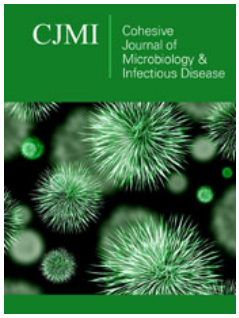

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Introduction

Infections caused by Carbapenemase Resistant Enterobacteriaceae (CRE) have been a growing concern in the United States as they pose a significant treatment challenge due to multi-drug resistance. In clinical practice, the old standard for CRE was combination treatment comprised of a carbapenem with an aminoglycoside, colistin, or tigecycline. Despite combination therapy, a treatment failure rate of 40-50% was reported [1]. This failure rate is attributed to the emergence of multi-drug resistant gram-negative bacilli producing advanced β-lactamases such as KPC (Klebsiella Pneumoniae Carbapenemase) and NDM (New Delhi Metallo-β-lactamase). Expression of NDM has been one of the most potent bacterial weapons against β-lactam antibiotics and exhibiting high resistance to conventional antibiotic therapy. Resistance has warranted the trial of novel more robust β-lactamase inhibitors such as vaborbactam with the conventional meropenem combined with other antibiotics in an attempt to conquer severe or life-threatening infections caused by resistant *Enterobacteriaceae* despite no available evidence of efficacy against NDM.

Case Presentation

In 2018, a patient in their twenties was admitted to a hospital in the United States with a chief complaint of fever and worsening respiratory distress. Medical history of this patient was positive for end-stage lung disease secondary to idiopathic pulmonary hypertension. Other conditions included: gastric ulcer, GERD, hypertension, history of inflammation of subcutaneous infusion site, primary pulmonary hypertension, right ventricular dilation, and epistaxis. The patient had no known drug allergies except for dermatitis with topical chlorhexidine. There was no pertinent surgical history. Family history included coronary artery disease and diabetes. No alcohol consumption or smoking was reported. The patient presented with an increase in the respiratory and heart rates and fever and chills. The patient developed sepsis secondary to MRSA bacteremia related to tunneled CVL infection and subsequently the line was removed after admission and source control was achieved. Blood cultures were positive for MRSA and when repeated 48 hours later were negative. Prior to admission, the patient had completed 14 days of vancomycin therapy for line infection. Vancomycin was initially chosen for MRSA treatment as the patient had good renal function. Cefepime was added on admission and later discontinued when blood culture showed no gram- negative growth. Blood cultures were negative for fungus, respiratory viral panel by PCR, and acid-fast bacillus. Despite therapeutic levels of vancomycin and MRSA susceptibility to it, the patient progressed to acute on chronic respiratory failure. ECMO (Extra - Corporeal Membrane Oxygenation) was started then a double-lung transplant was performed in which the patient underwent cardiopulmonary bypass with bicaval cannulation and vent placement. VAV-ECMO was re- initiated after that. Post-operatively, there was severe metabolic acidosis

and hemodynamic instability requiring vasopressors. Shortly afterwards, the patient returned to the operation room for chest hematoma evacuation.

Donor bronchus culture was negative. The patient's Broncho-Alveolar Lavage (BAL) culture was done one day after lung transplant and was positive for MRSA. Post-operatively, chest X-ray revealed persistent perihilar interstitial edema and retrocardiac airspace disease which was interpreted as atelectasis, infection, or inflammation. CT of the chest and abdomen reported multifocal pneumonia, bilateral pneumothoraces, and pulmonary arterial hypertension. TTE showed no vegetation. The patient experienced acute kidney injury and acute tubular necrosis in the setting of hypotension while on vancomycin (creatinine clearance approximately 30.9ml/min). Consequently, the Infectious Diseases Specialist switched vancomycin to linezolid and later to ceftaroline for MRSA coverage as the patient was thrombocytopenic. Cefepime was switched to piperacillin/tazobactam with nebulized tobramycin. As the patient was showing signs of infection, BAL culture was performed again 20 days post- lung transplant and was positive for *Enterobacter cloacae*. The Automated Susceptibility System (Vitek 2 bioMerieux) identified it as CRE positive. Carba-R-Cepheid detected NDM and KPC genes. No aspergillus was reported in the bronchial culture.

Enterobacter cloacae was overall susceptible to levofloxacin, ciprofloxacin, and amikacin. Kirby- Bauer and E-tests showed meropenem monotherapy as resistant, ceftazidime/avobactam as resistant, and meropenem/vaborbactam as intermediate with an MIC of 6mcg/mL. The FDA approved breakpoint for *Enterobacteriaceae* is less than or equal to 4mcg/mL [2]. Multi-drug resistant Enterobacter was treated with levofloxacin IV given every other day for a total of 8 doses starting with a dose of 750mg then 500mg every 48 hours combined with nebulized amikacin 250mg every 12 hours for 5 days. Intravenous levofloxacin was chosen over intravenous colistin due to renal impairment. After receiving one dose of IV levofloxacin and one dose of inhaled amikacin, the patient's clinical status was considered worse as assessed by the Pulmonologist based on increased pulmonary secretions. Accordingly, it was decided to administer meropenem/vaborbactam 1g IV every 12 hours for 15 days in combination with IV levofloxacin and nebulized amikacin as this was considered a life-threatening infection. In immunocompromised subjects with carbapenem resistant *Enterobacteriaceae* causing pneumonia, meropenem/vaborbactam was associated with higher clinical cure rates and a lower mortality rate than best available therapy [3,4].

Nebulized amikacin was switched to nebulized colistin 150mg every 12 hours for 33 more days. The doses of these antibiotics were appropriate as the patient was placed on hemodialysis 3 times a week throughout this time period and the doses were all administered post-dialysis. Infectious Diseases Society of America guidelines suggest that inhaled colistin may have potential pharmacokinetic advantages compared to inhaled polymyxin B. Clinical studies have also shown that inhaled colistin as an adjunct may be associated with improved clinical outcomes in the context of Ventilator Acquired Pneumonia (VAP) [5]. Therapeutic drug monitoring for levofloxacin using trough and peak values was performed with the third dose (at steady state). In vitro MIC for levofloxacin was reported as 1mcg/mL. Levofloxacin AUC 24 was calculated as greater than 100mg.hr/L. The AUC 24/MIC ratio of greater than 100 proved levofloxacin was at a therapeutic level. Additionally, the Clinical and Laboratory Standards Institute (CLSI) - M100 revised MIC breakpoints state that levofloxacin susceptibility breakpoint for *Enterobacteriaceae* is less than or equal to 1mcg/mL [6]. In the literature, meropenem/vaborbactam was reported effective in the treatment of KPC in particular [7].

However, pathogens expressing class B metallo- β -lactamases like NDM were excluded from preclinical and clinical trials as it was thought that NDM producing organisms are resistant to meropenem/vaborbactam. This left clinicians with no evidence-based antibiotic therapy for NDM-producing *Enterobacteriaceae*. In this case, the MIC of meropenem/vaborbactam was reported in vitro as 6mcg/mL. Meropenem/vaborbactam MIC breakpoints for *Enterobacteriaceae* are 4, 8, and 16mcg/mL for susceptible, intermediate, resistant, respectively [6]. Meropenem/vaborbactam trough concentration was done on day 4 of therapy and reported as 19.5mcg/mL. This result indicated that the trough was triple the MIC. Therefore, time above MIC was 100% rendering optimal therapeutic serum concentrations throughout. It was equivocal whether the patient clinically improved 24-48 hours post treatment initiation with meropenem/vaborbactam. However, the patient remained hemodynamically stable. Six days post-antibiotics, BAL culture was repeated and was negative. This suggested that the antimicrobials were effective in clearing *Enterobacter cloacae* from the lungs. After the antibiotic courses were completed in hospital, the patient was stable, was discharged home safely, and antibiotics were discontinued.

The reasons why antibiotics (levofloxacin, meropenem/vaborbactam, inhaled amikacin/colistin) were effective in clearing *Enterobacter cloacae* from the lungs in this case are unclear. A possible reason for clearance of *Enterobacter cloacae* is that the NDM gene was not expressed. Although Carba-R detected the presence of the NDM gene, there was no proof of translation into the beta-lactamase enzyme. For meropenem/vaborbactam, there is pharmacokinetic/pharmacodynamics data to support an MIC susceptibility breakpoint of 8mcg/mL for *Enterobacteriaceae*. The reported meropenem/vaborbactam MIC is 6mcg/mL. That could be a likely explanation of why the drug worked as indicated in the literature of E. Hirsch [6]. Additionally, at steady state, levofloxacin was at a therapeutic level and an MIC of 1mcg/mL was reported. A third possible explanation is based on new data showing that meropenem is synergistic when combined with colistin (15% synergy) in colistin-resistant *Enterobacteriaceae* [7,8]. Thus, inhaled colistin meropenem combination therapy may have promise as a treatment approach for patients infected with gram-negative respiratory pathogens harboring KPC and NDM. The addition of vaborbactam may have tipped the scale towards susceptibility to meropenem. Since 2018, antibiotic combinations

have further evolved and the newer β-lactams/β-lactamase inhibitors have become the cornerstone for CRE treatment due to better efficacy and less toxicity [9]. The Infectious Diseases Society of America guidelines changed to state that: "Ceftazidime-avibactam, meropenem-vaborbactam, and imipenem-cilastatin-relebactam are the preferred treatment options for KPC-producing infections outside of the urinary tract. Ceftazidime-avibactam in combination with aztreonam, or cefiderocol as monotherapy are preferred treatment options for NDM" [9]. Oral colistin should be avoided secondary to excessive nephrotoxicity and increased mortality.

Conclusion

In this unique case of post-bilateral lung transplant, severe nosocomial pneumonia ensued with BAL culture result positive for NDM and KPC-producing carbapenem resistant *Enterobacter cloacae*. Antibiotic therapy was switched to aggressively target Enterobacter pneumonia in the setting of high pulmonary complexity. Could pulmonary clearing of the organism and significant clinical improvement mean there might be potential benefit of trialing meropenem/vaborbactam combined with other antibiotics (instead of aztreonam) in NDM- producing *Enterobacteriaceae* infections? In case aztreonam is not a treatment option or not available, there might be a potential benefit of MV plus levofloxacin plus inhaled colistin combination as an alternative in NDM positive pneumonia. More studies are needed on the synergy between MV with levofloxacin or colistin.

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