Novel treatment approach to combat an infection with *Acinetobacter*

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The antimicrobial resistance of gram-negative pathogens has become problematic. In some cases related to *Pseudomonas spp.* and *Acinetobacter spp.*, no antimicrobials on the market can be utilized at standard doses. We report a case of resistant *Acinetobacter* infection in a patient in the intensive care unit. In this scenario, we successfully treated the infection with doripenem at a higher dose of 1 g with a 4-hour infusion time along with the combination of tigecycline and colistin.

The antimicrobial resistance of gram-negative organisms has become problematic in institutions across the United States. Two of the most common organisms implicated in these cases are *Pseudomonas spp.* and *Acinetobacter spp.* These organisms not only have a propensity to colonize patients who are on chronic ventilatory support but can also cause severe disease, such as bacteremia, pneumonia, and eventual sepsis (1, 2). No new effective antimicrobials have been specifically developed to combat these resistant organisms (3). *Acinetobacter*, a gram-negative coccobacillus, can resist nearly all antibiotics on the market through multiple resistance mechanisms (1, 4). Currently, the antimicrobials that can be utilized in some cases of *Acinetobacter* infection are sulbactam, carbapenems, aminoglycosides, tigecycline, and polymixin-based compounds (1, 4–6). Some of these agents can be used in different routes of administration to decrease bacterial burden (e.g., inhaled colistin) (7). In several cases, a combination of agents may be needed to target the pathogen through multiple sites of action (1). Another strategy is optimization of the pharmacodynamic parameters of antimicrobial agents (8). We report a case of resistant *Acinetobacter* that was treated with combination therapy and dose optimization of doripenem.

CASE STUDY

A 59-year-old African American woman was transferred to our intensive care unit (ICU) for continued ventilatory support after undergoing a Heller esophagomyotomy, left thoracotomy, Dacron graft repair of the aorta, and pleural flap closure of a segment of the esophagus. Prior to admission, she had been receiving nutrition and hydration through a percutaneous endoscopic gastrostomy tube due to achalasia refractory to multiple esophageal dilation procedures. Her initial complaint on

presentation to the emergency department was hematemesis and midepigastric pain with all feedings. The patient was taken to surgery 2 days after admission and subsequently required mechanical ventilation due to respiratory failure, which required eventual placement of a tracheostomy. After surgery, she also had multiple chest tube placements and developed an esophageal-pleural fistula. During this period, her fevers were treated with multiple regimens of antibiotics, including ampicillin/sulbactam, piperacillin/tazobactam, doripenem, tobramycin, vancomycin, and linezolid.

Two months after the initial surgery, the patient became febrile in the ICU with a temperature of 101.8°F. Cultures were obtained from the blood, sputum, urine, and drainage from the left chest tube. At that time the patient was on no antibiotics, and she was initiated empirically on levofloxacin 750 mg intravenously every 24 hours. Four days later, the culture from the chest tube drainage grew *Acinetobacter baumannii* that was susceptible to levofloxacin and tigecycline. An Etest (AB bioMérieux) indicated a minimum inhibitory concentration (MIC) of >32 mcg/mL to meropenem and >32 mcg/mL to doripenem. The patient's condition continued to deteriorate, and at that time levofloxacin was discontinued and she was started on doripenem 1 g infused every 8 hours with an infusion time of 4 hours, tigecycline 100 mg × 1 and then 50 mg every 12 hours infused over 1 hour, and colistin 2.5 mg/kg (150 mg) infused every 12 hours.

The patient continued to be febrile for the next 3 days. On day 9 (day 4 of antimicrobial therapy), a repeat left chest tube culture was performed and was negative for *Acinetobacter baumannii*. The antimicrobial regimen was continued for 15 days. During this time frame, the patient had no adverse events related to the antimicrobial therapy (e.g., renal dysfunction, seizures). Four days after discontinuing therapy, she continued to have intermittent fevers and was initiated on doripenem, linezolid,

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Disclosure: Dr. Stroup is a consultant for Ortho-McNeil-Janssen Pharmaceuticals, Inc.

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and caspofungin, but no organisms were isolated from the blood or chest tube cultures, and the drugs were subsequently discontinued. She was eventually discharged to home 6 months after her initial surgery on chronic ventilatory support.

DISCUSSION

Doripenem, a newer carbapenem on the market, was utilized in this case at a dose higher than recommended and at a prolonged infusion time. A case of resistant *Pseudomonas* ventriculitis successfully treated with doripenem 1 g every 8 hours in combination with tobramycin has been reported (9). Clinical success has also been documented with prolonged infusion times of 4 hours to increase the pharmacodynamic efficacy of doripenem compared with standard infusions of imipenem (10). Even though the MIC value was >32 in our patient, we elected to utilize the higher dosing scheme and prolonged infusion times based on pharmacokinetic and pharmacodynamic modeling studies that utilized this rationale for treatment (11).

We utilized both colistin and tigecycline in combination with doripenem. Colistin, a polypeptide antibiotic developed in the 1960s, has not been an antibiotic of primary use for several years due to its major adverse events, such as renal dysfunction (12, 13). This agent has recently been reintroduced for use in these resistant gram-negative infections. Colistin may be administered systemically or locally (12). We decided on systemic administration based on the premise that it could disrupt the bacterial cell membrane to allow the entrance of doripenem and thus increase our chances of killing the organism (1, 12). Our clinical microbiology lab did not make available the MIC of the organism to colistin. Colistin has also been utilized in combination with rifampin for *Acinetobacter* infections in past cases with some success (1).

Tigecycline, a newer glycylcycline antimicrobial, was used in this case based upon its efficacy in past case reports of *Acinetobacter* infection (14). Unfortunately, several case reports have also indicated that resistance quickly develops on tigecycline therapy, and there is currently some debate whether tigecycline, at standard doses, actually achieves concentrations in the lung to treat these highly resistant organisms (15–17). Due to the patient's comorbidities and risk of death, we elected to use this agent.

Although the organism in our case was sensitive to levofloxacin, we decided not to use it. No MIC to levofloxacin was reported by our laboratory for this isolate. The clinical deterioration on levofloxacin, past experience with this organism, and the lack of clinical data on levofloxacin as a primary treatment option were the main reasons we elected not to continue levofloxacin therapy. However, case reports of the successful treatment of meningitis caused by *Acinetobacter* spp. have been reported with fluoroquinolone-based therapies (18).

This case report provides an interesting solution to a problem that is becoming more prominent in hospital and long-term

care settings. We successfully treated a case of resistant *Acinetobacter* infection with the combination of high-dose, prolonged-infusion doripenem, colistin, and tigecycline.

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