Unique treatment approach for the treatment of a multidrug-resistant *Pseudomonas aeruginosa* infection

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INTRODUCTION

- Infections caused by antibiotic-resistant Gram-negative bacteria result in significant morbidity and mortality for patients as well as impact healthcare workers and caregivers. [1]
- Treatment of infections caused by Gram-negative organisms has become increasingly difficult due to antimicrobial resistance caused by multiple genetic and biochemical mechanisms.[2] In *Pseudomonas aeruginosa*, up-regulation of the MexAB-OprM efflux system results in reduced susceptibility to meropenem, fluoroquinolones, penicillins, and cephalosporins.[2] Mutations suppressing expression of OprD results in carbapenem permeability loss to *P. aeruginosa* strains.[2] Likewise, mutations leading to over production of the beta-lactamase AmpC result in resistance to anti-Pseudomonal penicillins and cephalosporins.
- Treatment of *P. aeruginosa* strains that develop resistance to multiple classes of antibiotics present significant challenges to the healthcare team. Colistimethate sodium (colistin), also known as polymyxin E, is a polypeptide antibiotic derived from *Bacillus polymyxa var. colistinus*.[3] Since its discovery in the 1940s, it has been used in the treatment of Gram-negative infections.[3] Colistin exhibits bactericidal activity and concentration-dependent killing with evidence of some post-antibiotic effect.[3] Its mechanism of action is unique in that it has lipophilic and hydrophilic moieties that interact electrostatically with the outer membranes of the Gram-negative bacteria.[3] This interaction displaces the divalent cations, calcium and magnesium, from the membranes of lipids that when disrupted release lipopolysaccharides.[3] This release changes the permeability of the bacterial membrane that leads to leakage of cell contents, cell lysis, and cell death.[3]
- Despite being limited by its significant adverse effects of nephrotoxicity and neurotoxicity, colistin is being prescribed more frequently due to an increase in resistant gram-negative infections and lack of newer antimicrobial agents.[6] Colistin is traditionally administered via intermittent intravenous infusion, but there is some data regarding its administration as an inhalation for direct delivery to the site of infection for pneumonia treatment.

CASE PRESENTATION

History of Present Illness

A 53 year-old male with a past medical history of atrial fibrillation was admitted to a multi-trauma intensive care unit (ICU) for an assault resulting in massive left sided hemothorax. He underwent a thoracotomy and was later discharged to an acute rehabilitation center. He returned from the rehabilitation center for fever and swelling over the thoracotomy incision. The patient underwent a second thoracotomy with the placement of chest tubes for drainage to manage an empyema in his pleural cavity. Two weeks into his ICU course, he developed hemodynamic changes consistent with sepsis and leukocytosis; therefore, cultures were obtained from his empyema and antibiotic therapy was started. Detailed culture and antibiotic data is provided below describing the development of resistance while on antibiotic therapy.

Table 1. Antibiotic Summary

Date Range	Antibiotic Administered
9/15 – 9/20	Meropenem IV
9/20 – 10/11	Piperacillin/tazobactam IV
9/24 – 9/26	Amikacin IV
9/30 – 10/18	Ciprofloxacin IV
10/7 – 10/11	Amikacin IV
10/11 – 10/18	Gentamicin IV
10/11 – 10/21	Cefepime IV
10/19 – 11/5	Colistimethate IV + Colistimethate Inhalation + Ceftazidime IV

CASE PRESENTATION

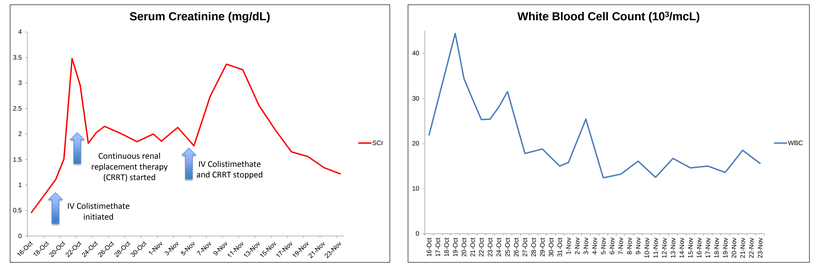
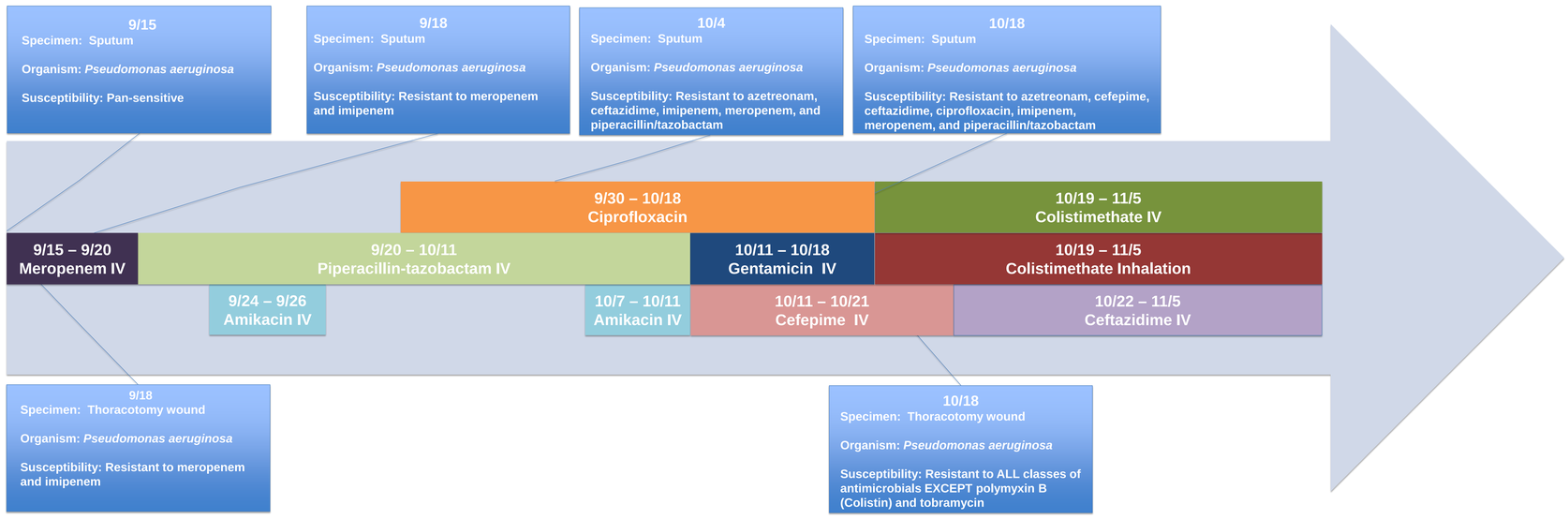


Figure 1. Trends in Serum Creatinine and White Blood Cell Count

Patient Outcome Summary

- After completion of ceftazidime IV, colistimethate IV and colistimethate inhaled therapy, the patient experienced clinical improvement and was able to be weaned from ventilatory support.
- The patient was eventually discharged from the intensive care unit and was admitted to a rehabilitation facility.
- The patient's sputum culture on discharge remained colonized with multidrug-resistant *Pseudomonas aeruginosa* but his clinical stability indicated that the antibiotic therapy he received in the intensive care unit suppressed his infection.

TIMELINE OF ANTIBIOTIC USE, CULTURE RESULTS, AND SENSITIVITY DURING ICU ADMISSION



DISCUSSION

- Antibiotic resistance is on the rise, threatening our capability to treat infectious diseases resulting in prolonged illnesses, increased risk of death and overall health care costs.
- Our patient case is a prime example this scenario. Over the course of three months, the organism causing his pulmonary infection developed resistance to multiple classes of antibiotics requiring the use of colistin, delivered by both the intravenous and inhalational route.
- This case report demonstrates the importance of the need for new treatment strategies and therapies to treat resistant gram-negative organisms.

REFERENCES

1. Boucher HW, Talbot GH, Benjamin DK et al. 10 X '20 Progress-development of new drugs active against gram-negative bacilli: an update from the infectious disease society of America. *Clinical Infectious Diseases;* 2013: 56 (12) 1685-94.
2. Rahal JJ. Antimicrobial resistance among and therapeutic options against gram-negative pathogens. *Clinical Infectious Diseases*; 2009:49:4-10.
3. Coly-Mycin M [package insert]. Rochester, MI: JHP Pharmaceuticals, LLC; 2013 Jan.
4. FDA. gov. Coly-Mycin M Parenteral. http://www.acessdata.fda.gov/drugsatfda_docs/label/2009/050108s026lbl.pdf (accessed 2015 Jun 17).
5. Berrazeg M, Jeannot K, Ntsogo VY et al. Mutations in beta-lactamase AmpC increase resistance of pseudomonas aeruginosa isolates to anti-pseudomonal cephalosporins. *Antimicrob Agents Chemother*; 2015.
6. Zhang H, Zhang Q. Clinical efficacy and safety of Colistin treatment in patients with pulmonary infection caused by pseudomonas aeruginosa or acinetobacter baumannii: a meta-analysis. *Med Sci.* 2013;11:34-42.