JPPT | Case Report

Clearance of Persistent *Staphylococcus aureus* Bacteremia in a Preterm Neonate With the Use of Combination Cefazolin and Ertapenem

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Late-onset sepsis caused by *Staphylococcus aureus* is a serious and relatively common complication encountered by preterm neonates in NICUs. Typical treatment regimens for invasive methicillin-sensitive *Staphylococcus aureus* (MSSA) include semisynthetic beta lactam antibiotics, such as nafcillin. This report describes the first use of a combination of cefazolin and ertapenem to successfully treat persistent MSSA bacteremia in a preterm neonate who failed traditional first-line therapy.

ABBREVIATIONS DOL, day of life; MIC, minimum inhibitory concentration; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-sensitive *Staphylococcus aureus*; NICU, neonatal intensive care unit; PBP, penicillin-binding protein

KEYWORDS antibiotic; bacteremia sepsis; cefazolin; ertapenem; neonate; preterm; *Staphylococcus aureus*

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Introduction

Late-onset sepsis continues to be a serious complication encountered by premature neonates. Recognition of this burden has continued since the 2002 report from the National Institute of Child Health and Human Development (NICHD) showed a 21% incidence of late onset sepsis in very low birth weight neonates (birth weight < 1500 g), with current rates similar and stable.[1,2] Late-onset sepsis is defined as infection occurring after 48 to 72 hours of life. Of the causative organisms, *Staphylococcus aureus* is responsible for 2% to 8% of late-onset bacteremia.[1,3,4] Because the incidence of methicillin-resistant *Staphylococcus aureus* (MRSA) infections has risen over time in neonates in the NICU setting, significant attention has been paid to investigations surrounding infection control policies and novel antimicrobial therapies with which to target MRSA infections. Even though the incidence of MRSA infection is rising, infection with methicillin-sensitive *Staphylococcus aureus* (MSSA) is still 3 to 4 times more common in neonates in the NICU.[3–5] Furthermore, there is renewed recognition that infections caused by MSSA can be as severe as those caused by MRSA; they are potentially mediated by acquisition of virulence factors and may be more likely associated with persistent blood stream infection.[3]

Treatment of suspected invasive *Staphylococcus* infections begins with removal of in-dwelling catheters or devices (if possible), examination for the source of focal infection, and antibiotic therapy.[3] According to the American Academy of Pediatrics *Red Book: 2018 Report of the Committee on Infectious Diseases,* empiric antibiotic regimens used when methicillin susceptibility is unknown include vancomycin alone or in combination with nafcillin, depending on the severity of infection. Once methicillin sensitivity has been determined, then antibiotic therapy can be narrowed to nafcillin or cefazolin. Alternatives presented in the *Red Book* for treatment of MSSA include clindamycin, vancomycin, and ampicillin combined with sulbactam; however, these medications are only indicated in patients with penicillin allergy or polymicrobial infections with susceptible isolates. In cases of persistent bacteremia or those associated with in-dwelling devices, rifampin can be added to the therapeutic regimen.[6] This report follows the *CARE Guidelines*[7] to describe the first use of a combination of cefazolin and ertapenem as salvage therapy to successfully treat persistent MSSA bacteremia in a low birth weight preterm neonate with continued bacteremia despite treatment with nafcillin monotherapy and then nafcillin combined with rifampin. This treatment regimen, which was informed by a case report describing the clearance of persistent MSSA bacteremia in an elderly woman, was chosen owing to the severity of the patient's illness and persistent bacteremia.[8] This combination of cefazolin and ertapenem has not been previously reported in neonates and warrants further study because it may decrease morbidity and mortality in this vulnerable population.

Case

A 1510-g female twin neonate was born by cesarean section at 29-0/7 weeks' gestation to a 28-year-old mother because of progressive preterm labor and

breech presentation. The pregnancy was complicated by dichorionic-diamniotic twin gestation and preterm premature rupture of membranes at 24-3/7 weeks' gestation. Antenatally, the mother was treated with latency antibiotics, azithromycin and cephalexin, as well as a course of corticosteroids. At delivery, the neonate required positive pressure ventilation for resuscitation, with resultant Apgar scores of 5 and 7 at 1 and 5 minutes, respectively. Following initial resuscitation, her first week of life was complicated by respiratory failure managed by surfactant administration, inhaled nitric oxide, and high-frequency oscillatory ventilation. Umbilical arterial and venous catheters were in place. As part of her initial management, one blood culture was obtained according to our NICU practice, which demonstrated no bacterial growth, and she completed a 48-hour course of empiric antibiotic therapy with ampicillin and gentamicin. Nutritionally she was managed with decreasing total parenteral nutrition, while enteral nutrition with donor human milk was increased. She was receiving no other daily medications. The Figure displays a timeline of the clinically relevant events in the case.

On day of life (DOL) 9, the neonate had an acute worsening of her clinical status manifested by poor perfusion. Laboratory evaluation demonstrated a mixed metabolic/respiratory acidosis, new-onset leukocytosis with polymorphonuclear cell predominance (25,600 cells/μL, 86% polymorphonuclear cells), and C-reactive protein elevation (24.8 mg/L; reference rage: <8.0 mg/L). A chest radiograph demonstrated a new left upper lobe infiltrate. Blood cultures were obtained from a peripheral site and the umbilical venous catheter, and empiric antibiotic therapy was started with vancomycin and gentamicin. Blood cultures demonstrated growth of MSSA from the umbilical venous catheter and antibiotic therapy was narrowed to nafcillin. Minimum inhibitory concentrations, which were determined using an automated Vitek 2 microbial identification system with GP-67 card, are presented in the Table. Nafcillin was initially dosed at 50 mg/kg/day, divided every 12 hours, but this dose was increased rapidly to 99 mg/kg/day, divided every 8 hours after just 2 administrations of the lower dose because of persistent bacteremia.

Daily blood cultures were obtained starting from the clinical worsening on DOL 9 and were persistently positive for MSSA through DOL 17. The umbilical venous catheter was removed with initial positive cultures, and therapy was administered through a peripheral IV. The patient had no other indwelling lines, only a peripheral IV. To investigate for a possible nidus of infection leading to persistently positive blood cultures, transthoracic echocardiogram, vena cava duplex ultrasound, and abdominal ultrasound studies were completed. A lumbar puncture was not performed secondary to thrombocytopenia. These studies did not reveal an uncontrolled source for ongoing bacteremia. Given this, the dose of nafcillin was escalated (DOL 12, 50 mg/kg/day, divided every 12 hours; DOL 13, 99 mg/kg/day, divided every 8 hours; and DOL 15, 200 mg/kg/day, divided every 8 hours). Additionally, rifampin was added on DOL 14 (10 mg/kg/day, divided every 12 hours). Despite this escalation of therapy, blood cultures drawn every day remained positive for 9 days.

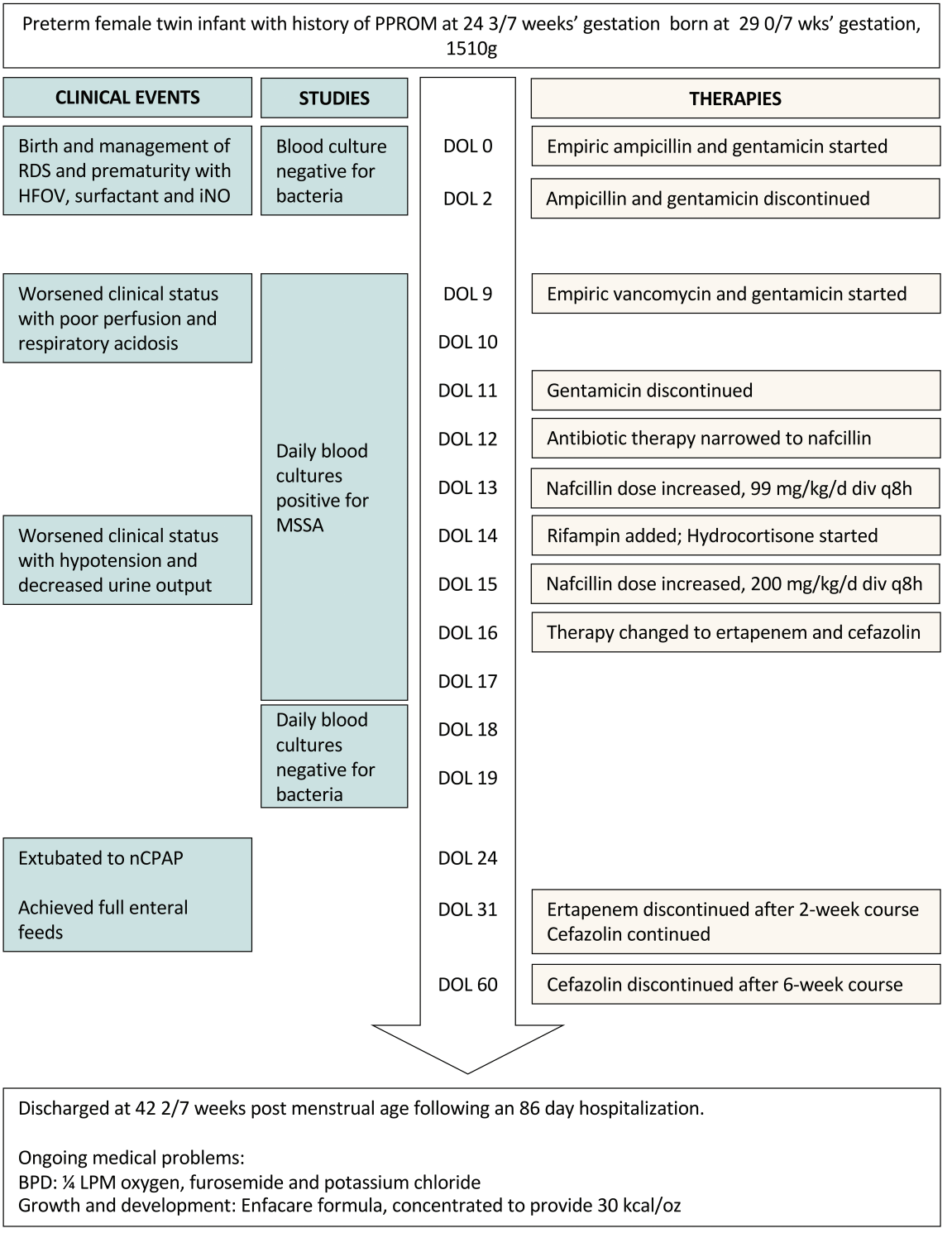
On DOL 14, the neonate began to have low blood pressures, decreased urine output, and enlarged T-waves on telemetry monitoring. Laboratory evaluation demonstrated the following electrolyte abnormalities: sodium = 123 mmol/L; potassium = 10 mmol/L; chloride = 95 mmol/L; carbon dioxide = 18 mEq/L; blood urea nitrogen = 18 mg/dL; creatinine = 1.18 mg/dL; glucose = 42 mg/dL; and calcium = 8.1 mg/dL. In addition to volume resuscitation and vasopressor support with dopamine, hyperkalemia was managed with calcium gluconate, sodium bicarbonate, furosemide, and insulin with dextrose. Given the constellation of signs and laboratory findings, adrenal crisis was included in the differential diagnosis of this clinical change, and hydrocortisone (1 mg/kg/dose every 8 hours) treatment was initiated. With the addition of hydrocortisone, laboratory values normalized, but because of the severity of this clinical deterioration and persistent bacteremia, on DOL 16, after 8 days of antibiotic therapy, treatment was changed to a combination of ertapenem (15 mg/kg/dose, every 12 hours) and cefazolin (50 mg/kg/dose, every 8 hours). On DOL 18, following 30 hours of combination antibiotic therapy with ertapenem and cefazolin, blood cultures became negative. A 2-week course of combination therapy was completed followed by 4 additional weeks of cefazolin monotherapy.

The neonate was discharged following an 86-day hospitalization at 42-2/7 weeks' postmenstrual age. Her ongoing medical problem at discharge was bronchopulmonary dysplasia managed with supplemental oxygen and diuretic therapy.

Discussion

In this case, combination antimicrobial therapy using cefazolin and ertapenem successfully cleared persistent MSSA bacteremia in a low birth weight preterm neonate. Despite increasing the dose of single-agent nafcillin and combining nafcillin with a second-line agent, rifampin, blood cultures in this neonate remained positive for MSSA. This persistent bacteremia and a further clinical deterioration that was concerning for adrenal crisis led to the decision to use combination therapy with cefazolin and ertapenem. While linezolid was also considered for salvage therapy, the neonate had thrombocytopenia at the time (platelet count 87,000 cells/μL), and because of the known side effect of thrombocytopenia with linezolid use, linezolid was not chosen. With the combination of these 2 antibiotics, MSSA was quickly cleared from the blood, and therapy was completed over a 6-week course with no adverse effects.

Figure. Case timeline for important clinical events. Clinical events surrounding changes in the patient's condition are presented in chronologic order according to the DOL in the left-most column. Pertinent laboratory investigations are presented to the right of the clinical events. Finally, medical therapies are presented in the right-most column.



BPD, bronchopulmonary dysplasia; DOL, day of life; HFOV, high-frequency oscillatory ventilation; iNO, inhaled nitric oxide; LPM, liters per minute; MSSA, methicillin-sensitive Staphylococcus aureus; nCPAP, nasal continuous positive airway pressure; PPROM, preterm premature rupture of membranes; RDS, respiratory distress syndrome

Table. Minimum Inhibitory Concentration Values for Antibiotics Tested Against the *Staphylococcus aureus* Isolate in this Case

Antibiotic	MIC, mg/L	Interpretation
Oxacillin	0.5	Sensitive
Gentamicin	<0.5	Sensitive
Clindamycin	*	Resistant
Linezolid	2	Sensitive
Vancomycin	<0.5	Sensitive
Tetracycline	>16	Resistant
Trimethoprim/sulfamethoxazole	<10	Sensitive

* MIC not provided by the microbiology laboratory.

To date, there is only one other report of this particular combination therapy in clinical practice. In 2016, Sakoulas et al[8] described the case of an 80-year-old female patient with multiple medical comorbidities and MSSA bacteremia. Following 5 days of single-agent cefazolin therapy and persistently positive blood cultures, ertapenem was added to the antimicrobial regimen. Within 24 hours after initiation of combination therapy, blood cultures were negative for MSSA. This patient completed 2 weeks of combination therapy followed by an additional 4 weeks of cefazolin monotherapy. We followed this same treatment regimen and duration in our case. The authors went on to investigate the combination of cefazolin and ertapenem using several *in vitro* and murine-based *in vivo* techniques. In these studies, cefazolin and ertapenem worked in synergy to promote bacterial lysis, reduce biofilm formation, and enhance innate immune system bacterial killing. In their murine subcutaneous-infection model,[8] only combination therapy with cefazolin and ertapenem reduced MSSA colony-forming units.

Use of dual beta-lactam therapy has been documented in the literature for both Gram-negative and Gram-positive bacterial infections. Examples of this include empiric use of cefotaxime and ampicillin for bacterial meningitis, use of ampicillin and ceftriaxone for *Enterococcus* endocarditis, and use of dual carbapenem therapy for carbapenemase-producing *Klebsiella* pneumonia.[9–11] Beta-lactam antibiotics exhibit bactericidal activity by binding to penicillin-binding proteins (PBPs) and interfering with bacterial cell wall synthesis, leading to cell lysis. Theoretically, the use of 2 beta-lactam agents may increase binding and affinity to multiple PBPs, leading to better efficacy than can be achieved with the individual drugs alone.[8,12] Studies[12–14] have shown that even among drugs of the same class, affinities for the different PBPs vary, and affinities for the same drug will differ for different organisms. Additionally, an animal model demonstrated that decreasing the neutrophil count in a *Staphylococcus aureus* abscess enhanced bacterial killing with cefazolin in rats; the authors[15] postulated that this could be a result of alterations in PBPs in the presence of a high neutrophil count.

Unfortunately, despite many complicated infections in the NICU setting in which carbapenem antibiotics may be useful, there exist limited data in the literature regarding pharmacokinetics and pharmacodynamics in neonates. Currently, only imipenem is approved from birth onward, with indications for meropenem and ertapenem beginning in infants greater than 3 months of age, and despite doripenem not having any on-label indications in children. For a detailed review of studies on carbapenem pharmacokinetics and pharmacodynamics in neonates, the reader is referred to a 2014 review by Pacifici and Allegaert.[16]

Our report adds a second observation of the successful use of combination cefazolin and ertapenem to treat persistent MSSA bacteremia. Although there is a vast difference in the ages between our patient and the one reported by Sakoulas et al,[8] both had remarkable clearing of their infection within 24 to 30 hours of initiation of combination therapy. *Staphylococcus aureus* infections continue to be a significant source of mortality and morbidity in premature neonates. Continuing to investigate treatment strategies is critical, especially in cases of persistently positive blood cultures. At this time, there are no clinical trials evaluating the combination of cefazolin and ertapenem. The potential for this combination therapy of cefazolin and ertapenem to treat MSSA infection and reduce morbidity and mortality warrants further study.

ARTICLE INFORMATION

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Ethical Approval and Informed Consent Given the nature of this study, the project was exempt from institution review board/ethics committee review and informed consent was not required.

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