The Use of Daptomycin in the Treatment of Persistent Coagulase-Negative Staphylococcal Sepsis in Premature Infants: A Case Series

Suzan S. Asfour, MscPharm; Raneem S. Asfour, PharmD; Thanaa M. Khalil, MD; and Mountasser M. Al-Mouqdad, MD

OBJECTIVE Daptomycin is a lipopeptide antibiotic with rapid bactericidal activity against Gram-positive bacteria. Reports regarding the use of daptomycin in infants are still limited. Thus, the objective of this report is to describe the safety and efficacy of daptomycin in premature infants with persistent coagulase-negative staphylococci (CoNS) infection.

METHODS This was a retrospective chart review of 10 premature infants with persistent CoNS infection who received daptomycin therapy between January 2018 and September 2019. Four patients had endocarditis and 1 had bacterial meningitis and infectious endocarditis. The other 5 patients had persistent CoNS bacteraemia only.

RESULTS Daptomycin treatment was successful for 5 patients. The others died owing to multiple factors such as prematurity, sepsis, and chronic lung disease. Adverse drug reactions, including elevation of creatine phosphokinase and/or hepatotoxicity, were noted in 4 patients.

CONCLUSIONS Large and randomized studies are necessary to ensure daptomycin's safety and efficacy for the treatment of infants with persistent sepsis caused by Gram-positive bacteria.

ABBREVIATIONS ALT, alanine aminotransferase; AST, aspartate aminotransferase; BW, birth weight; BPD, bronchopulmonary dysplasia; CLABSI, central line-associated bloodstream infection; CVC, central venous catheter; CoNS, coagulase-negative staphylococci; CPK, creatine phosphokinase; FDA, US Food and Drug Administration; GA, gestational age; IVH, intraventricular hemorrhage; MIC, minimum inhibitory concentration; NEC, necrotizing enterocolitis; NICU, neonatal intensive care unit; PICC, peripherally inserted central catheter; PPHN, persistent pulmonary hypertension; ROP, retinopathy of prematurity; UAC, umbilical arterial catheter; UVC, umbilical venous catheter

KEYWORDS bacteraemia; case report; coagulase-negative staphylococcal; daptomycin; infection; premature infants; sepsis

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Introduction

Gram-positive organisms including coagulase-negative staphylococci (CoNS) are the most common causative organisms of late-onset sepsis in premature infants.¹ The incidence of CoNS in NICUs is 44%.² Of the CoNS reported in the NICU, *Staphylococcus epidermidis* has been reported to be the most common causative organism with an incidence of 80.7%.² Despite vancomycin being the drug of choice for the treatment of serious CoNS infections, its expanded use could result in an increase in the MIC, which could result in the organisms becoming less responsive to vancomycin.³ Hence, there is a need for other medications for the treatment of CoNS. Thus far, the alternatives have been limited to linezolid and daptomycin.^{4,5} In 2017, daptomycin was approved by the FDA for treating complicated skin and skin structure infections and for bacteraemia caused by *Staphylo-*

coccus aureus in pediatric patients older than 1 year; however, it was not approved for use in neonates and infants.⁶ Unfortunately, limited literature is available regarding the use of daptomycin for treating neonates and infants.^{7,8} Herein, we report our clinical experience with the use of daptomycin for the treatment of severe CoNS infection in premature infants.

Materials and Methods

Study Design and Population. This study was conducted at the NICU of the Hospital of Paediatrics in King Saud Medical City where, on average, 1100 patients are admitted to the NICU, including NICU levels 2 and 3. We included neonates who received daptomycin for the treatment of persistent CoNS infections between January 2018 and September 2019.

Definitions. CoNS Bacteraemia. One positive blood culture for a patient with an intravascular line in the pres-

ence of clinical sepsis and laboratory abnormalities.⁹

Persistent CoNS Bacteraemia. Presence of three repeated positive blood cultures despite receiving effective antibiotic therapy with an appropriate dose based on culture sensitivity and MIC results, obtained at least 48 hours apart, caused by the same organism in combination with laboratory abnormalities and clinical signs of sepsis.⁹ In addition, echocardiography, lumbar puncture, and urine culture were performed if other sources of infection were suspected.

Appropriate Vancomycin Dosing. The initial vancomycin dose was calculated based on NeoFax. Trough level was drawn before the fifth dose. The vancomycin dose was adjusted later according to the serum drug level.

Good Serum Drug Concentration. The desired range of trough serum vancomycin concentrations for persistent CoNS infections was 10 to 20 mg/L, depending on infection site. Serum concentration of daptomycin was not measured.

Adequate Therapy Duration. Appropriate dose of vancomycin for minimum 7 days.

Concomitant Antibiotic. Any antibiotic administered at any time during exposure to daptomycin.

Daptomycin Dosing: 10 mg/kg/dose once daily^{7,10} or 6 mg/kg/dose every 12 hours.⁸

Antimicrobial Susceptibility Test. The VITEK 2 system (bioMérieux, Marcy-l'Etoile, France) was used for antibiotic susceptibility testing and identification of isolates. MIC values of vancomycin and daptomycin were analyzed using this system and at times using a standard E-test as an additional test for daptomycin. The results were compared with values provided in the Clinical and Laboratory Standards Institute guidelines as breakpoint references.

Hepatotoxicity. Hepatotoxicity was defined as liver injury caused by exposure to drugs and was associated with an increase in alanine aminotransferase (ALT) level by more than 5 times the upper limit of normal or 3 times from elevated baseline.^{11,12}

Clinical Outcome. Successful treatment with daptomycin was defined as the resolution of microbial infection with no clinical or laboratory evidence of infection during the daptomycin therapy.

Data Collection and Follow-up. We retrospectively reviewed all the included patients' charts from the time of NICU admission until discharge or death. Demographic and clinical data, source of infection, culture results, isolated pathogen, age at onset of daptomycin treatment, daptomycin dose, duration of treatment, concomitant antibiotic treatments with daptomycin, and outcome data were obtained for all neonates. Depending on the severity of the case, assessment of renal function (serum creatinine and blood urea nitrogen) and creatine phosphokinase (CPK), liver function (ALT, aspartate aminotransferase [AST], total bilirubin, and direct bilirubin) were performed daily or twice

weekly during the course of daptomycin therapy. In addition, skin rashes, phlebitis, and anaphylactic reactions were documented before and after the initiation of daptomycin.

Results

During the study period, the patients received intravenous daptomycin for the treatment of severe infections with CoNS. All included patients (8 boys, 2 girls) were premature infants. The median gestational age was 27 weeks (range, 24–35), and the median birth weight was 1030 grams (range, 750–2275). Eight patients were born in our hospital. The median length of hospital stay was 75 days (range, 43–134). A summary of patients with persistent CoNS infections is provided in Table 1.

The median age at the onset of the first positive persistent CoNS bacteraemia was 14.5 days (range, 7–40 days), and the age at the start of daptomycin therapy was 39 days (range, 14–62). All reported CoNS were 100% resistant to cefazoline and cloxacillin. The median level of the highest vancomycin MIC during vancomycin therapy was 1 (range, 1–2), whereas daptomycin was susceptible with a MIC < 0.5. All patients received total parenteral nutrition, and 9 of the 10 patients were on mechanical ventilation during persistent infection with CoNS. Seven out of 10 cases were diagnosed as central line-associated bloodstream infections (Table 1).

All patients initially received vancomycin with or without rifampin, but vancomycin was discontinued in all patients before daptomycin was started (Table 1). Seven patients received linezolid with or without rifampin and before daptomycin (Table 2). Meropenem was added for 2 patients because infection with Gram-negative bacteria was suspected. Amikacin was added for 1 patient owing to *Klebsiella* blood infection, and 1 patient received levofloxacin at the initiation of treatment with daptomycin owing to *Stenotrophomonas* infection from a bronchial wash. Cefotaxime was added for 1 patient owing to *Klebsiella* infection from a bronchial wash (Table 1). Six neonates received daptomycin (Cubicin; Laboratoires Merck Sharp & Dohme-Chibret, Riom, France) in doses of 6 mg/kg/dose every 12 hours, and 4 received 10 mg/kg every 24 hours. Daptomycin at a concentration of 5.6 mg/mL was administered over 60 minutes via either peripheral or central line. Six patients required inotropic support.

All patients had abnormal laboratory findings. The median baseline C-reactive protein, white blood cell count, and platelet counts prior to daptomycin therapy were 86.7 mg/L (range, 12.9–115), 5.92/mm³ (range, 1.60–12.28/mm³), and 25.5,000/mm³ (range, 11–170,000/mm³), respectively. Serum CPK was measured in 9 patients and was increased in 2 of these patients. The median value of the highest CPK was 91

Table 1. Demographic Characteristics and Clinical Features of the 10 Patients Treated With Daptomycin

Patient No.	GA, wk	BW, g	Underlying Problems	Type of Catheter	Age at the Start of Daptomycin, Days	Daptomycin Dosage	Daptomycin Duration, Days	Concomitant Antibiotics	Isolated Bacteria	Outcome
1	29	1500	Prematurity, sepsis, grade I IVH, seizure, NEC, BPD	None	37	10 mg/kg every 24 hr	4	Rifampin	<i>S epidermidis</i>	Death
2	27	750	Preterm, CLABSI, ROP, BPD	PICC	40	6 mg/kg every 12 hr	29	none	<i>S epidermidis</i>	Discharge
3	25	760	Prematurity, CLABSI, grade III IVH, seizure, perforated NEC, pneumothorax, BPD	PICC	47	6 mg/kg every 12 hr	18	Rifampin	<i>S epidermidis</i>	Death
4	24	780	Prematurity, sepsis, endocarditis, grade II IVH, seizure, ROP, BPD	None	56	6 mg/kg/ every 12 hr	5	None	<i>S capitis</i>	Death
5	28	1200	Prematurity, CLABSI, endocarditis, BPD	UVC	14	6 mg/kg every 12 hr	31	Rifampin Meropenem	<i>S epidermidis</i>	Discharge
6	27	1100	Prematurity, CLABSI, endocarditis, meningitis, grade IV IVH, seizure, ROP, BPD	PICC	38	10 mg/kg every 24 hr	44	none	<i>S epidermidis</i>	Discharge
7	35	2275	Small bowel obstruction, CLABSI, endocarditis, BPD	CVC	26	6 mg/kg every 12 hr	29	Rifampin Amikacin	<i>S epidermidis</i>	Discharge
8	25	750	Prematurity, grade II IVH, sepsis, spontaneous perforation, BPD	None	55	6 mg/kg every 12 hr	1	levofloxacin	<i>S epidermidis</i>	Death
9	34	2025	Gastroschisis, CLABSI, PPHN	PICC	62	10 mg/kg every 24 hr	19	Meropenem	<i>S epidermidis</i>	Death
10	26	960	Prematurity, CLABSI, endocarditis, grade III IVH, NEC, BPD	PICC	33	10 mg/kg every 24 hr	42	Rifampin Cefotaxime	<i>Shaemolyticus</i>	Discharge

BPD, bronchopulmonary dysplasia; BW, birth weight; CLABSI, central line-associated bloodstream infection; CVC, central venous catheter; GA, gestational age; IVH, intraventricular hemorrhage; NEC, necrotizing enterocolitis; PICC, peripherally inserted central catheter; PPHN, persistent pulmonary hypertension; ROP, retinopathy of prematurity; UVC, umbilical venous catheter

Table 2. Treatment Regimens of 10 Patients Treated With Vancomycin/Linezolid

Patient No.	Vancomycin						Linezolid	
	Age at the Start of Therapy, Days	Dose	Serum Trough Concentration, mg/L	MIC at Beginning of Therapy	Highest MIC During Therapy	Duration, Days	Age (Days) at the Start	Duration of Therapy, Days
1	7	15 mg/kg every 8 hr	10.83	2	2	8	16	20*
2	13	20 mg/kg every 6 hr	19.1	1	2	18*	32	7*
3	6	10 mg/kg every 8 hr	17.62	1	1	34	41	5
4	43	15 mg/kg every 6 hr	23	2	2	12*	None	None
5	1	15 mg/kg every 8 hr	12.2	1	1	13	None	None
6	15	15 mg/kg/ every 8 hr	22.47	0.5	1	16*	32	5
7	10	15 mg/kg every 6 hr	10.3	1	1	15*	None	None
8	8	15 mg/kg every 6 hr	15.2	1	1	41*	50	4
9	16	10 mg/kg every 6 hr	11.42	1	1	38	55	6
10	12	15 mg/kg every 8 hr	15.6	1	2	10	23	9*

* Rifampin given.

U/L (range, 24–366). No increase in serum creatinine or blood urea nitrogen was noted. Before starting daptomycin, the median baseline values of ALT, AST, total bilirubin, and direct bilirubin levels were 41.2 U/L (range, 11.8–232.3), 88.9 U/L (range, 19.4–440.8), 227 μ mol/L (range, 49.8–509.8), and 211.9 μ mol/L (range, 44–415.9), respectively. The highest median of ALT, AST, total bilirubin, and direct bilirubin levels during daptomycin therapy were 109.45 U/L (range, 25.20–1144), 258.4 U/L (range, 115.1–1115), 632.9 μ mol/L (range, 169.6–802.5), 291.95 μ mol/L (range, 150.4–608.5), respectively. In 3 patients, the ALT level was higher than 100 U/L before starting daptomycin, and 1 of the 3 developed severe hepatotoxicity and died on the second day of daptomycin administration. ALT levels normalized during daptomycin therapy in the remaining patients. Another patient had a normal ALT level prior to daptomycin therapy and then developed mild hepatotoxicity at the end of the course (Figure). The remaining patients did not have any adverse effects related to daptomycin therapy, but owing to suspected sepsis, 1 patient needed antibiotics (amikacin and cloxacillin) 1 week after stopping the daptomycin regimen. Although 5 patients died because of persistent invasive infection and daptomycin treatment failure, treatment was successful in the remaining 5 patients.

Discussion

Daptomycin, a cyclic lipopeptide antibiotic approved by the FDA for the treatment of severe sepsis due to Gram-positive bacteria, acts by destroying the bacterial cellular membrane and inhibiting protein synthesis.¹³ Initially, daptomycin was used to treat infectious endocarditis, meningitis, and skin infections in adults¹⁴; however, it is now being used as an alternative treatment for pediatric infections caused by vancomycin-resistant enterococci.^{15,16} However, data are limited regarding the use of daptomycin in the treatment of severe and persistent neonatal sepsis caused by Gram-positive bacteria.

Previously, we published a case report of successful treatment of infective endocarditis caused by *Staphylococcus haemolyticus* in premature infants.⁷ Recently, a systematic review on the safety and efficacy of daptomycin in the pediatric population was published.¹⁷ The review suggested that daptomycin is safe, well tolerated, and effective in the treatment of infections caused by Gram-positive bacteria.

In this case series, we report 10 cases of neonatal sepsis with persistent CoNS infections treated with daptomycin. CoNS were the most commonly isolated organisms and were susceptible to vancomycin and

Figure. Trends of alanine aminotransferase levels during daptomycin therapy.

▲ Patient 1; ■ Patient 2; ▲ Patient 3; ● Patient 4; ● Patient 5; ● Patient 6; □ Patient 7; ■ Patient 9; ◆ Patient 10

Patient 8 had two ALT values. The first at baseline (101.2 U/L) and the second 2 days after daptomycin therapy (1144 U/L).

linezolid.² Vancomycin is an effective antibiotic for the treatment of serious staphylococcal infections; therefore, we initiated vancomycin therapy for all patients. In some patients, vancomycin was administered in combination with rifampin or linezolid.

Two studies have shown that the combination of vancomycin and rifampin has a synergistic influence on methicillin-resistant CoNS and *S aureus*.^{18,19} Rifampin has specific lipophilic properties that enable it to penetrate biofilms. However, there is a high probability of resistance developing if it is used singly; therefore, rifampin has been prescribed in combination with vancomycin.²⁰ Linezolid has been approved by the FDA for treating infections with Gram-positive bacteria in the pediatric population. Many studies have shown that linezolid is as effective as vancomycin in the treatment of sepsis due to resistant CoNS.^{21,22} However, linezolid is bacteriostatic against most susceptible organisms; therefore, it is not used in patients with infective endocarditis.²³

Whether rifampin or linezolid should be added in the case of our patients was considered after 3 repeated positive blood cultures were obtained at least 48 hours apart and after a discussion with a pediatric infectious disease consultant. Blood cultures positive for the same organism were obtained, and the MIC increased in some patients despite the administration of an appropriate dose of vancomycin, targeted serum drug concentrations for an adequate period, and combined treatment with other antibiotics, such as linezolid or rifampin. Center et al²⁴ reported a decrease in the

susceptibility of CoNS to vancomycin with increasing in MIC even if cultures were sensitive to the drug.

Fifty percent of the infants died, probably owing to sepsis or multiple factors such as prematurity, sepsis, and chronic lung disease. Liver function test, CPK, and renal function test results obtained before and after daptomycin initiation were studied. We noticed a significant increase in ALT result in only 1 patient; the results were unchanged in the remaining patients. Limited data are available regarding the most appropriate dose of daptomycin for the treatment of persistent CoNS neonatal sepsis. Case reports account for most of the related literature, and in all these cases, 6 mg/kg/dose every 12 hours or 10 mg/kg/dose once daily of daptomycin was administered. Six of our patients received the first regimen, and we did not find any change in the efficacy between the 2 regimens. It should be noted that the patients who developed hepatotoxicity received the first regimen.

The strong points in our case series are as follows. To our knowledge, this is the first report describing daptomycin use in premature neonates with persistent CoNS infections. Both regimens of daptomycin dosing (6 mg/kg/dose every 12 hours versus 10 mg/kg/dose once daily) were included in this case series. Finally, patients with sepsis included in the study developed either meningitis or infectious endocarditis in addition to bacteraemia. There are also some noteworthy limitations. This was a case series with a small number of patients. Furthermore, patients' data were collected

retrospectively. Finally, daptomycin serum concentrations was not determined.

Conclusions and Recommendations

Our case series is an extension of our case report⁷ and serves to confirm the efficacy of daptomycin in the treatment of persistent CoNS neonatal sepsis. When used, we recommend a dose of 10 mg/kg once daily. Daptomycin should be prepared to a concentration of 5.6 mg/mL and infused over 60 minutes. We recommend monitoring renal and hepatic function, and CPK once weekly at least. On the basis of our findings, we recommend that a large and randomized controlled trial should be conducted to determine the appropriate dose and safety of daptomycin for the treatment of infants with persistent sepsis caused by Gram-positive bacteria.

Article Information

Affiliations. Clinical Pharmacy Department (SSA), King Saud Medical City, Riyadh, Saudi Arabia; Pharmacy College (RSA), Jordan University of Science and Technology, Irbid, Jordan; Obstetrics and Gynecology Department (TMK), King Saud Medical City, Riyadh, Saudi Arabia; Neonatal Intensive Care Unit (MMA), King Saud Medical City, Riyadh, Saudi Arabia.

Correspondence. Mountasser Al-Mouqdad, MD; m.almouqdad@ksmc.med.sa

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