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CASE REPORT

Bloodstream Infection Due to a VIM-Metallo-β-Lactamase-Producing *Klebsiella pneumoniae* Treated with Cefiderocol in a Preterm Newborn

Caterina Monari · Ferdinando Spagnuolo · Mariantonietta Pisaturo · Serena Ascione · Giovanna Donnarumma · Federica Calò · Elisabetta Caredda · Fortunato Montella · Anna Maietta · Paolo Montaldo · Umberto Pugliese · Massimiliano Galdiero · Mauro Carpentieri · Nicola Coppola

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ABSTRACT

Background: The prevalence of certain multidrug-resistant organisms (MDROs), especially Gram-negative bacteria, is dramatically increasing in patient care settings, including pediatric and neonatal units. However, most of the new drugs available for the treatment of MDROs have not yet been studied in children and newborns.

Case report: We report the clinical case of a preterm neonate, born at 31 weeks gestation + 1 day of age by emergency Cesarean Section (CS), with a bloodstream infection (BSI) due to a Verona integron-borne metallo-β-lactamase (VIM)-producing *Klebsiella pneumoniae*. We successfully treated the infection with cefiderocol in an *off-label* regimen at the following dose: loading dose 60 mg/kg and then 40 mg/kg every 8 h in extended infusion for 9 days. The baby showed a quick clinical and biochemical improvement and tolerated well the treatment. Follow-up blood cultures at 48 h after the start of cefiderocol were negative.

Conclusions: Antimicrobial-resistant pathogens are of increasing concern in neonatal settings. More studies in this unique population are necessary to better describe the pharmacokinetic and pharmacodynamic profile of the new drugs against MDROs, such as cefiderocol, and to define a proper effective dose.

Keywords: MDROs; Newborn; Cefiderocol; Antimicrobial stewardship program (ASP); Infection prevention and control (IPC)

C. Monari · M. Pisaturo · F. Calò · N. Coppola (✉)
Department of Mental Health and Public Medicine - Infectious Diseases Unit, University of Campania Luigi Vanvitelli, Via L. Armanni 5, 80131 Naples, Italy
e-mail: nicola.coppola@unicampania.it

F. Spagnuolo · S. Ascione · E. Caredda · A. Maietta · P. Montaldo · U. Pugliese · M. Carpentieri
Neonatal Intensive Care Unit, University of Campania Luigi Vanvitelli, Naples, Italy

G. Donnarumma · F. Montella · M. Galdiero
Department of Experimental Medicine, Microbiology Section, University of Campania "Luigi Vanvitelli", Naples, Italy

Key Summary Points

Several new drugs are available for the treatment of infections caused by multidrug-resistant organisms (MDROs), especially Gram-negative bacteria. However, most of the new drugs available for the treatment of MDROs have not yet been studied in children and newborns.

We report the clinical case of a preterm neonate, born at 31 weeks gestation + 1 day of age by emergency Cesarean section, with a bloodstream infection (BSI) due to a Verona integron-borne metallo-β-lactamase (VIM)-producing *Klebsiella pneumonia* and successfully treated with cefiderocol in an *off-label* regimen.

INTRODUCTION

Antimicrobial resistance (AMR) is one of the main healthcare threats globally in recent decades, significantly increasing the overall hospital mortality rate, the need for intensive care units (ICUs), the length of stay in hospital, and healthcare costs [1]. According to the World Health Organization (WHO) estimates, of the 700,000 deaths caused yearly by multidrug-resistant organisms (MDROs) across all ages around the world, 214,000 were attributable to newborns [2, 3]. However, studies focusing on the global burden of AMR among children and neonates are still lacking.

The overuse and misuse of antibiotics around the world is worsening the AMR phenomenon not only among adults but also in the pediatric setting [2, 4–6]. Several studies have suggested that half of antibiotics used in both inpatient and outpatient pediatric settings are not indicated [7–9]. Furthermore, the prevalence of certain MDROs, especially Gram-negative (MDR-GN) bacteria, is dramatically increasing in patient care settings, including pediatric and neonatal units [10–14], with consequently higher morbidity and mortality rates [12, 15].

Newborns, especially if born preterm, are at a high risk of infection because of the immature immune system, prolonged hospitalization, and use of invasive devices [10]. Moreover, in these patients the treatment of infections caused by MDROs is particularly challenging, since most of the new drugs available for the treatment of MDROs have not yet been studied in children and newborns, and their use is often off-label.

We report the clinical case of a preterm newborn with a bloodstream infection (BSI) due to a Verona integron-borne metallo-β-lactamase (VIM)-producing *Klebsiella pneumoniae* treated with cefiderocol.

CASE REPORT AND DISCUSSION

A female preterm neonate, born at 31 weeks gestation (GA) + 1 day of age by emergency Cesarean section (C-section) due to maternal pre-eclampsia (Apgar index 7 at minute 1 and 8 at minute 5), with a birth weight of 1100 g, was admitted to the neonatal intensive care unit (NICU) soon after delivery on July 19, 2022. The mother suffered from gestational diabetes treated with a balanced, healthy diet. The baby showed a fetal growth restriction until the 26th week of GA.

In the first days after birth, the baby needed non-invasive supplementary oxygen therapy through CPAP (continuous positive airway pressure) with FiO2 of 21%. Given the prematurity, in accordance with national protocols the baby received routine antibiotic therapy with ampicillin/sulbactam and netilmicin. However, she was later exposed to meropenem, because of drug intolerance. The therapy was administered through an epicutaneo-cava catheter, which was positioned on the fifth day of life.

On day 20 (33 weeks + 6 days adjusted GA), the newborn showed a worsening of clinical conditions, with feeding intolerance and bradycardia. An increase in white blood cell counts (20,000/mm^3), C-reactive protein (CRP, five times upper limit of normal, ULN), and procalcitonin (PCT, 14 ng/ml) and a decrease in

Table 1 Clinical, biochemical, and microbiological data before and during cefiderocol treatment

	Day of admission	Day of BSI	Day +2	Day +7	EOT
Heart rate, BPM	130	126	132	135	130
RR/min	60	58	65	55	60
SpO_2, %	96	97	98	98	98
Oxygen supplementation, yes/no	Y	N	N	N	N
Temperature, °C	36.2	36.5	36.4	36.7	36.5
WBC cells/mm^3 (according to age)	7190	20,610	15,690	11,110	14,220
PLT cells/mm^3 (150,000–450,000)[a]	150,000	63,000	155,000	202,000	291,000
Creatinine, mg/dl (0.3–1)	0.69	0.55	0.46	0.35	0.44
Total bilirubin, mg/dl (according to age)	1.8	3.1	3.8	2.5	4.28
CRP, times ULN (< 1)	0.03	1.79	3.4	0.38	0.08
PCT, ng/ml (< 0.5)	NA	14	2.04	NA	0.18
Blood cultures, result	Negative	Positive	Negative	Negative	Negative

BSI blood stream infection, *EOT* end of treatment, *BPM* beats per minute, *RR* respiratory rate, *SpO_2* peripheral oxygen saturation, *Y/N* yes/no, *WBC* white blood cells, *PLT* platelet count, *CRP* C-reactive protein, *ULN* upper limit of normal, *PCT* procalcitonin, *NA* not available

[a]Range of normal values in brackets

platelet count (65,000/mm^3) were observed. Arterial blood cultures were immediately obtained, the central catheter was removed, and an empirical antibiotic treatment with vancomycin and netilmicin was started. In a few hours, *K. pneumoniae* group and the production of VIM metallo-beta-lactamase, as a mechanism of resistance, were detected by fast GenMark Dx ePlex system (GenMark Diagnostics, Inc., Carlsbad, CA, USA) identification panels for Gram-positive, Gram-negative, and *Candida* species.

The baby was hemodynamically stable, and the weight was 1300 g. In accordance with the infectious disease consultant, cefiderocol in monotherapy as an off-label regimen was started at a dose of 60 mg/kg loading dose, followed by 40 mg/kg every 8 h in extended infusions (3–4 h long), according to the single paper in the literature regarding the dose of cefiderocol in pediatric subjects [16]. In accordance with the Ethic Committee of the University of Campania L. Vanvitelli, we obtained the parents' written consent for the use of cefiderocol in an *off-label* regimen. Moreover, isolation precautions were rapidly put in place, according to the infection prevention and control (IPC) program of our hospital. In order to avoid a VIM-producing *K. pneumoniae* cluster in the NICU, the patient and all the neonates hospitalized in the unit in the same period were screened for carbapenem-resistant Enterobacterales (CRE). The rectal swab of the patient showed an intestinal colonization by extended-spectrum beta-lactamase (ESBL)-producing *K. pneumoniae* and *Pseudomonas aeruginosa*. Another neonate developed a positive rectal swab for the same strain of *K. pneumonia*. She was admitted to the NICU 2 days after patient 1 had a bloodstream infection (BSI), and her rectal swab was positive for a VIM-producing *K. pneumoniae* 7 days after admission to the NICU, but she did not develop a CRE infection. No other patient had intestinal CRE.

The patient's initial blood culture confirmed the presence of *K. pneumoniae* using the Maldi-

Tof MS system (Bruker; Berlin, Germany). The phenotypic antibiogram performed with the BD Phoenix™ M50 system (Becton Dickinson, Franklin Lakes, NJ, USA) showed intermediate susceptibility to imipenem (minimum inhibitory concentration, MIC 4 mg/l), resistance to ertapenem (MIC 1 mg/l), and susceptibility to cefiderocol (MIC 0.125 mg/l), according to EUCAST criteria 2022. The molecular antibiogram confirmed the identification of VIM-metallo-β-lactamases (MBL) by the Xpert Carba-R test, performed using the GeneXpert platform (Cepheid; Sunnyvale, CA, USA).

Clinical, biochemical, and microbiological data during antimicrobial therapy are shown in Table 1. The baby showed a quick improvement in clinical conditions and biochemical values and tolerated the antibiotic treatment well. As early as 48 hours after the start of cefiderocol, we observed a decrease in white blood cells (15,690/mm^3), and inflammatory markers (CRP three times ULN, PCT 2 ng/ml). Platelet count increased and reached normal values, i.e., 155,000 cell/mm^3 (normal range 150,000–450,000). Follow-up blood cultures were performed 48 h after the introduction of the active therapy and resulted negative. Inflammatory markers continued to decrease and became negative after 5 days of therapy. We discontinued cefiderocol at day 9 of therapy. Fourteen days after the BSI, the patient was in good clinical condition, but still hospitalized because of prematurity issues and feeding intolerance.

Our paper reports the case of a preterm newborn (31 weeks + 1 day GA) with a BSI due to a VIM-producing *K. pneumoniae* successfully treated with cefiderocol in an *off-label* regimen. Thanks to rapid microbiology techniques, we were able to start active antibiotic therapy a few hours after the worsening of the clinical conditions.

To date, cefiderocol is an antibiotic indicated for the treatment of infections due to aerobic Gram-negative organisms in adults with limited treatment options at a dose of 2 g every 8 h [17]. The safety and efficacy of the drug in children below 18 years of age have not yet been established [17]. No data are available on the dose in children, especially in neonates, nor have case reports been described in the literature. Only Katsube et al., in a poster published in 2019, suggested a pediatric dose of cefiderocol in subjects from birth to less than 18 years of age, developing a pharmacokinetic (PK) model in children relying on PK data from adults [16]. In order to provide adequate exposure, colleagues proposed a dose based on age and body weight. From 3 months to 18 years, the dose of 60 mg/kg (maximum 2 g) every 8 h (q8h) was selected as a standard dose. The dose for infants aged less than 2 months was adjusted according to gestational age: below 32 weeks GA, 30 mg/kg q8h; above or equal to 32 weeks GA, 40 mg/kg q8h.

According to this PK model, since no other case reports on the use of cefiderocol in neonates were available, we decided to use the following dose of cefiderocol in an off-label regimen, considering the adjusted GA (33 weeks + 6 days GA): 60 mg/kg as the loading dose and then 40 mg/kg every 8 h in extended infusion of 3 hours. We decided to use cefiderocol in monotherapy since the patient was hemodynamically stable. Moreover, a source control, i.e., removal of the midline, had already been performed. The therapy was well tolerated and was associated with a quick clinical response, suggesting that this important antibiotic may also be used in the neonatal population with infections caused by MDR-GN bacteria.

Neonates admitted to NICUs are at a high risk of bacterial infections, especially MDR infections, for several causes: prematurity, immature immune system, prolonged hospitalization, and frequent need for invasive devices and antibiotics. Despite the global attention given to MDR infections in adults, data on the current burden of AMR in children and especially neonates are still scanty. An increasing rate of MDR-GN infections in neonatal units has been described in the literature [12, 18, 19]. In particular, a recent narrative review by Flannery et al. reported a worrisome emergence of ESBL-producing *Enterobacterales* and carbapenem-resistant *Enterobacterales* in neonatal settings [10]. Colleagues described a variable ESBL intestinal colonization rate: from 5% in the USA [8] to 9.6% in Portugal [20], and a range from 49% to 85.9% in low- to middle-income

countries [21–23]. Regarding the intestinal colonization by carbapenem-resistant organisms, the reported rates are less frequent: from 2.6% in Turkey [24] to 7.5% and 8.7% in Cambodia [25] and India [23], respectively, and 9.2% in China. A systematic review conducted by Ding et al. in 2019, describing the antibiotic susceptibility profile of carbapenem-resistant *Enterobacteriaceae* responsible for neonatal sepsis in China, reported 39 isolates of *Klebsiella pneumoniae* and *Escherichia coli* resistant to carbapenems out of a total of 740 Gram-negative isolates in neonates (39/740, 5.3%) [19]. Genotypic characteristics were available for 21 isolates (20 *K. pneumoniae*, 1 *E. coli*). The most frequently reported genotype was *New Delhi–metallo-betalactamase* (NDM-1, 81.0%), followed by KPC-2 (9.5%) and IMP-4 (9.5%). Moreover, in 15 isolates, ESBL (66.7% carried TEM and SHV genotypes, 80.0% CTX-M), and in 7 AmpC genes were detected.

Many risk factors have been associated with colonization and infection caused by MDROs in newborns [10]. Among them, prematurity (below 37 weeks GA), birth weight below 1500 g, prolonged hospitalization (15 days or more), mechanical ventilation, central venous catheters, and invasive devices are the most frequently reported [13, 26–29]. Other important risk factors are physical proximity to other patients with MDRO infection/colonization, cumulative exposure to antibiotics, prior exposure to third-generation cephalosporins and carbapenems, maternal colonization, understaffing and overcrowding in NICUs, hand hygiene, and poor IPC measures [24, 26, 28, 30–32]. In fact, horizontal dissemination is the most commonly reported source of an MDR-GN outbreak [31].

Overuse and misuse of antibiotics contribute to the acquisition and spread of infections due to antibiotic-resistant bacteria [5, 6]. It is estimated that misuse of antibiotics in NICUs may be as high as 20–50% [33]. To tackle the emergence of resistance, regulatory authorities and scientific societies have published international guidelines that recommend the implementation of Antibiotic Stewardship Programs (ASPs) in both adult and pediatric hospitals, with the aim of improving the appropriateness of antibiotic prescriptions, including the indication, choice of molecule, route of administration, and duration of therapy [9, 34–37]. Already in 2016 the Infectious Diseases Society of America (IDSA) suggested the implementation of Antimicrobial Stewardship (AS) interventions to reduce inappropriate antibiotic use and resistance rate in NICUs [37]. In 2020, experts from the Centers for Disease Control and Prevention (CDC) defined the prevention of MDR-GN infections as a top pediatric research priority [9, 10].

CONCLUSIONS

We report the first case of a newborn treated with cefiderocol for a BSI due to a VIM-producing *K. pneumoniae*, with an excellent clinical response and tolerability. More studies in this unique population are necessary to better describe the pharmacokinetic and pharmacodynamic profile of the new drugs against MDROs, such as cefiderocol, and to define a proper effective dose.

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Disclosures. The authors, Nicola Coppola, Caterina Monari, Mariantonietta Pisaturo, Mauro Carpentieri, Ferdinando Spagnuolo, Federica Calò, Serena Ascione, Elisabetta Caredda, Anna Maietta, Paolo Montaldo, Umberto Pugliese, Giovanna Donnarumma, Fortunato Montella, and Massimiliano Galdiero, have nothing to disclose.

Compliance with Ethics Guidelines. We have obtained the parents' written consent for the publication of this case report. All procedures performed in this study were in accordance with Ethics Committee of the University of Campania L. Vanvitelli, Naples and with the 1964 Helsinki declaration and its later amendments or comparable ethics standards.

DATA AVAILABILITY

Not applicable.

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