Levofloxacin Use in the Neonate: A Case Series

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We report 6 cases of intravenous levofloxacin use to treat multidrug-resistant nosocomial respiratory infections in neonates with a postmenstrual age ranging from 27 to 42 weeks. Because of a lack of neonatal-specific information for levofloxacin, the usual pediatric dosage (10 mg/kg per dose every 12 hours) was used in these patients. Clinical cure occurred in 5 of the 6 patients. Only minimal short-term adverse effects were noted.

ABBREVIATIONS CRP, C-reactive protein; DOL, day of life; ETT, endotracheal tube; NICU, neonatal intensive care unit; TMP-SMX, trimethoprim-sulfamethoxazole; UOP, urine output

KEYWORDS infant; levofloxacin; multidrug-resistant infection; neonate; newborn

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Introduction

Multidrug-resistant organisms continue to cause increased morbidity and mortality worldwide because of challenges in treating these infections with currently available and commonly used antibiotics.¹ Neonatal patients in the intensive care unit are particularly susceptible to serious infections caused by multidrug-resistant, Gram-negative organisms. Reasons for this include prematurity, prolonged hospitalization, presence of central venous catheters, parenteral nutrition, prior antibiotic therapy, and invasive procedures, such as mechanical ventilation or urinary catheterization.^{2,3}

Stenotrophomonas and *Chryseobacterium* are 2 organisms that are increasingly prevalent nosocomial pathogens in the neonatal intensive care unit (NICU) because of their intrinsic resistance to antibiotics, including β -lactams and aminoglycosides commonly used in this setting.^{4–6} *Stenotrophomonas maltophilia* is a non-lactose-fermenting, Gram-negative aerobic bacillus, previously known as *Xanthomonas maltophilia* or *Pseudomonas maltophilia*. *Chryseobacterium* belongs to the family Flavobacteriaceae and is a Gram-negative, aerobic, non-fermentive, oxidase-positive, and catalase-positive non-motile bacilli. Nosocomial infections in the NICU due to multidrug-resistant organisms are leading neonatal clinicians to use classes of antibiotics, such as fluoroquinolones, that have not been well studied in this patient population.

Fluoroquinolones are proven to be effective for a wide range of infections due to both Gram-positive and Gram-negative organisms. However, because of premarketing reports on fluoroquinolone-associated arthropathy in animal studies, use in the pediatric population was not recommended.⁷ Since then, approved indications have expanded to include some pediatric indications, and there is growing use of fluo-

roquinolones in neonates, particularly ciprofloxacin.^{8–11} Although literature describing the use of levofloxacin in the neonatal patient is limited to case reports,¹² there are circumstances when this medication is required because of the resistance pattern of the organism, clinical deterioration with first-line treatment, medication shortages, or other factors that preclude the use of alternative antibiotics, such as the risk of kernicterus with trimethoprim-sulfamethoxazole (TMP-SMX), for example.

In order to expand the available evidence in the neonatal patient population, we report a case series of patients who were treated with levofloxacin (5 mg/mL in D5W injection, Hospira, St-Laurent, QC, Canada) in 4 NICUs across Canada.

Case Series

Informed consent was obtained from the parents of each neonate included in this case series. All of the patients received multiple cultures and courses of antibiotics (Tables 1–6). Unless otherwise stated, antibiotic dosage followed recommendations appropriate for postmenstrual and postnatal age in Lexicomp (Pediatric and Neonatal Lexi-Drugs),¹³ Neofax,¹⁴ American Academy of Pediatrics Red Book,¹⁵ or the primary literature^{16–19} in a few cases. Antibiotics were adjusted as needed based on renal function and serum drug concentration. Vancomycin doses were adjusted as required to achieve serum concentrations of 10 to 20 mg/L. TMP-SMX dosage was based on the TMP component used to treat pneumonia and ranged from 15 to 20 mg/kg/day.

Case 1. Patient 1 was a male born at 39 weeks' gestational age and with a birth weight of 2390 g, with intrauterine growth restriction and congenital diaphragmatic hernia. At birth, he required intubation

Table 1. Clinical Course of Neonate Described in Case 1

DOL	Culture	Organism	Sensitivity	Antibiotics
0	Blood	No growth		AMP, CTX × 7 days; GEN × 1 dose
7	ETT	<i>Stenotrophomonas maltophilia</i> ; <i>Pseudomonas aeruginosa</i>	LVX, TMP-SMX CAZ, GEN, CIP, TZP, TOB	TZP, TMP-SMX × 6 days
	Blood	No growth	N/A	
12	ETT	No growth		CAZ, LVX × 6 days
24	ETT	<i>S maltophilia</i>	LVX, CHL, TMP-SMX, TGC	
26	Blood	No growth		VAN × 2 days LVX × 14 days
29	ETT	<i>S maltophilia</i>	Same as previous	
65	Sputum	No growth		

AMP, ampicillin; CAZ, ceftazidime; CHL, chloramphenicol; CIP, ciprofloxacin; CTX, cefotaxime; DOL, day of life; ETT, endotracheal tube; GEN, gentamicin; LVX, levofloxacin; TGC, tigecycline; TMP-SMX, trimethoprim/sulfamethoxazole; TOB, tobramycin; TZP, piperacillin/tazobactam; VAN, vancomycin

and was empirically treated with 7 days of antibiotics, including ampicillin 150 mg/kg/day divided every 8 hours and a single dose of gentamicin (5 mg/kg) that was subsequently switched to cefotaxime (100 mg/kg/day divided every 12 hours) for an initially low urine output, which resolved quickly (Table 1). On day of life 7 (DOL 7) his sputum culture showed heavy neutrophils and Gram-negative bacilli on Gram stain, and antibiotic coverage was broadened to include intravenous (IV) piperacillin/tazobactam (200 mg/kg/day piperacillin component divided every 12 hours) and TMP-SMX (15 mg/kg/day trimethoprim component divided every 12 hours). C-reactive protein (CRP) on DOL 8 was elevated at 38.8 mg/L. The final sputum culture grew moderate *S maltophilia* and scant *Pseudomonas aeruginosa*. After 5 days (DOL 12) on this treatment, chest X-ray showed increased atelectasis of the right upper lobe, white blood cell count had increased from $7.6 \times 10^3/\mu\text{L}$ to $8.8 \times 10^3/\mu\text{L}$, neutrophils had increased from 3.7 to $5.2 \times 10^9/\text{L}$, and platelets had remained stable. The patient went for repair of his diaphragmatic hernia on this day, but postoperatively his ventilator settings remained high. Based on the NICU team's concerns regarding the chest X-ray and ventilator requirements, antibiotic coverage was switched to levofloxacin 10 mg/kg IV every 12 hours and ceftazidime (150 mg/kg/day divided every 8 hours) to treat presumed ventilator-associated pneumonia. Of note, a sputum culture taken this day showed no growth. After 3 days of therapy he was given a single dose of hydrocortisone and was extubated to continuous positive airway pressure 3 days later. Antibiotics were discontinued on the recommendation of infectious disease consultants (as completed a total of 10 days of therapy for *Stenotrophomonas*).

Unfortunately, 6 days after stopping antibiotics he deteriorated and required reintubation (DOL 24). Levofloxacin 10 mg/kg IV every 12 hours and vancomycin

(45 mg/kg/day divided every 8 hours) were empirically started. Vancomycin was discontinued after 48 hours when sputum culture results showed moderate *S maltophilia*. At this point, white blood cell (neutrophil) counts were elevated at $24.6 (11.8) \times 10^3/\mu\text{L}$ ($\times 10^9/\text{L}$), and platelets were normal. Eight days after starting levofloxacin, sputum cultures were clear. Levofloxacin therapy was continued, and he improved clinically, with CRP decreasing from 36.7 mg/L on day 1 to 17.2 mg/L on day 4 of therapy. After 14 days of levofloxacin, antibiotics were stopped. He was extubated and did not require reintubation or any further antibiotic treatment.

The patient tolerated both courses of levofloxacin therapy well. Blood pressure and serum glucose remained stable throughout treatment, and the infant had no recorded cardiac concerns. Vitals, electrolytes, hepatic enzymes, blood gases, and serum glucose were monitored as per typical NICU practice. Renal function markers, including urine output, blood urea nitrogen, and serum creatinine, were within normal limits throughout the duration of both treatment courses. No diarrhea or any other adverse effects were documented. On DOL 65 a sputum culture showed no growth. This patient was transferred to a general pediatrics unit at DOL 77 and was discharged home at 6.5 months of age.

Case 2. Patient 2 was a dichorionic diamniotic twin male delivered at 28 weeks' gestational age and with a birth weight of 1072 g. He was intubated shortly after birth because of poor respiratory effort, and he received 48 hours of empiric antibiotics using ampicillin (150 mg/kg/day divided every 8 hours) and tobramycin (5 mg/kg every 36 hours) because of a shortage of gentamicin (Table 2). He was extubated on DOL 2. On DOL 24 vancomycin (45 mg/kg/day divided every 8 hours) and cefotaxime (150 mg/kg/day divided every 8 hours) were started for suspected sepsis and pneumonia because of increased oxygen requirements and desaturations.

Table 2. Clinical Course of Neonate Described in Case 2

DOL	Culture	Organism	Sensitivity	Antibiotics
0	Blood	No growth	NA	AMP, TOB × 2 days
24	Blood	No growth	NA	VAN, CTX × 6 days
44	None—surgical prophylaxis for patent ductus arteriosus ligation			CFZ × 2 days
45	ETT	<i>Stenotrophomonas maltophilia</i>	LVX, TMP-SMX	MEM × 7 days
		<i>Enterobacter cloacae</i>	CIP, GEN, TMP-SMX	TMP-SMX × 17 days
		<i>Citrobacter freundii</i>	Same as <i>Enterobacter</i>	
	Blood	No growth		
51	ETT	<i>S maltophilia</i>	Same as previous	(TMP-SMX continuing)
		<i>Klebsiella pneumoniae</i>	CFZ, GEN, TOB, TZP, TMP-SMX	
	Blood	No growth		
57				LVX 8 days
58	ETT	<i>S maltophilia</i>	Same as previous	
75	ETT	<i>S maltophilia</i>	Same as previous	

AMP, ampicillin; CFZ, cefazolin; CIP, ciprofloxacin; CTX, cefotaxime; DOL, day of life; ETT, endotracheal tube; GEN, gentamicin; LVX, levofloxacin; MEM, meropenem; TMP-SMX, trimethoprim-sulfamethoxazole; TOB, tobramycin; TZP, piperacillin/tazobactam; VAN, vancomycin

This therapy was continued for 6 days. On DOL 43 he was intubated in preparation for ligation of a patent ductus arteriosus, which occurred the following day. Serial chest X-rays on DOLs 43 to 44 described increasing bilateral lower lobe consolidation. A sputum culture drawn on DOL 45 grew moderate *Enterobacter cloacae*, moderate *Citrobacter freundii*, and moderate *S maltophilia*. White blood cell (neutrophil) count was low at $5.2 (0.9) \times 10^3/\mu\text{L}$ ($\times 10^9/\text{L}$), platelets were normal, and no CRP was drawn. He was started on meropenem (60 mg/kg/day divided every 8 hours) for empiric coverage of *Enterobacter* and *Citrobacter* and TMP-SMX (20 mg/kg/day trimethoprim component divided every 12 hours) on DOL 48; CRP on this day was elevated at 49.6 mg/L. A repeat sputum culture on day 4 of this therapy grew scant *Klebsiella pneumoniae* in addition to moderate *Stenotrophomonas*. Meropenem was continued for 7 days because of the NICU team's discomfort with narrowing coverage, and TMP-SMX continued. He was extubated, but his oxygen requirements increased and he continued to have creamy secretions.

Nine days after starting TMP-SMX (DOL 57), the infectious disease consult team recommended that levofloxacin 10 mg/kg IV every 12 hours be added for the management of ventilator-associated pneumonia. CRP, white blood cells, and neutrophil counts had normalized at this point. A repeat sputum culture taken 2 days later had moderate neutrophils and grew scant *Stenotrophomonas*. He completed 17 days of TMP-SMX and 8 days of levofloxacin. Blood pressure and serum glucose values remained stable throughout treatment, and the infant had no recorded cardiac concerns. Vitals, electrolytes, hepatic enzymes, blood gases, and serum glucose were monitored as per typical NICU practice. The infant tolerated the levofloxacin well without any

adverse effects reported. Renal function (UO, BUN, and SCr) remained within normal limits.

He was extubated on DOL 65, 1 day after completion of antibiotics, but only remained extubated for 20 minutes before he required reintubation. A sputum culture on DOL 75 showed scant neutrophils and *Stenotrophomonas*, but antibiotic therapy was not initiated because there were no clinical signs of pneumonia, and lab indicators of infection were normal. No further sputum cultures were done during this admission. He would go on to have antibiotic therapy for necrotizing enterocolitis as well as another failed attempt at extubation. Finally, after pretreatment with hydrocortisone on DOLs 78 to 85, and dexamethasone on DOLs 85 to 88, he was successfully extubated on DOL 89. He was transferred to a general pediatrics unit after a 4-month stay in NICU and was discharged to home at 5.5 months of age.

Case 3. Patient 3 was a female born via cesarean delivery at 28 + 5/7 weeks' gestational age with a birth weight of 634 g (small for gestational age). She was intubated shortly after birth. Empiric antibiotics were started on DOL 1 because of an unexpected manipulation of the umbilical venous catheter and were administered for 48 hours (Table 3). On DOL 9, antibiotics were initiated (vancomycin 30 mg/kg/day divided every 8 hours, gentamicin 2.5 mg/kg every 18 hours × 2 days then switched to cefotaxime 100 mg/kg/day divided every 12 hours) and were continued for 10 days to treat necrotizing enterocolitis. Ventilator-associated pneumonia was diagnosed on DOL 30, with the chest X-ray showing a right upper lobe opacification. The oxygen requirements had increased, CRP concentrations increased from 4.2 to 93 mg/mL, and a complete blood count showed a left shift of 69%. The white blood

Table 3. Clinical Course of Neonate Described in Case 3

DOL	Culture	Organism	Sensitivity	Antibiotics
1	Blood	No growth		AMP, GEN × 2 days
9	Blood	No growth		VAN, CTX × 7 days
30	Blood	<i>Staphylococcus capitis</i>	VAN	VAN × 14 days CTX × 2 days, then GEN × 10 days
		<i>Staphylococcus aureus</i>	CFZ, CLX, CLI, VAN, TMP-SMX	
	ETT	<i>Klebsiella pneumoniae</i>	CFZ, P/T, TOB, GEN, TMP-SMX	
		<i>Acinetobacter</i> species	MEM, TOB, GEN, TMP-SMX	
38	ETT	<i>Chryseobacterium indologenes</i>	LVX, CIP, TMP-SMX	
		<i>K pneumoniae</i>	LVX, CIP, CFZ, TZP, TOB, GEN, TMP-SMX	
40	ETT	<i>Chryseobacterium</i> species	Same as previous	MEM × 4 days, then TMP-SMX × 1 day, then LVX × 14 days
		<i>K pneumoniae</i>	Same as previous	
52	ETT	<i>C indologenes</i>	CAZ, TZP, TMP-SMX	
60	ETT	<i>C indologenes</i>	CAZ, TZP, TMP-SMX	LVX × 2 days, then CAZ × 8 days
		<i>K pneumoniae</i>	CFZ, TZP, TOB, GEN, TMP-SMX	
	Urine	<i>Enterococcus faecalis</i> 2 MCFU/L	AMP, VAN	VAN × 10 days
		<i>Staphylococcus</i> species <1 MCFU/L	Not reported	

AMP, ampicillin; CAZ, ceftazidime; CFZ, cefazolin; CIP, ciprofloxacin; CLI, clindamycin; CLX, cloxacillin; CTX, cefotaxime; DOL, day of life; ETT, endotracheal tube; GEN, gentamicin; LVX, levofloxacin; MCFU, mega colony-forming units; MEM, meropenem; TMP-SMX, trimethoprim-sulfamethoxazole; TOB, tobramycin; TZP, piperacillin/tazobactam; VAN, vancomycin

cell count continued to increase until DOL 35, when it peaked at $75.5 \times 10^3/\mu\text{L}$. Antibiotic therapy was initiated with vancomycin (30 mg/kg/day divided every 8 hours) and cefotaxime (150 mg/kg/day divided every 8 hours) to provide broad-spectrum coverage. Dexamethasone was also started in an attempt to reduce ventilator requirements, and was continued for a 10-day course. The antibiotics were changed to vancomycin (30 mg/kg/day divided every 8 hours) and gentamicin (2.5 mg/kg every 18 hours) when blood cultures showed *Staphylococcus capitis* and endotracheal tube (ETT) aspirates grew *Staphylococcus aureus*, *K pneumoniae*, and *Acinetobacter* species.

On DOL 38, day 8 of antibiotic therapy, ETT cultures were obtained for continued large oxygen requirements, and the Gram stain showed Gram-negative bacilli, so meropenem (90 mg/kg/day divided every 8 hours) was added. The ETT culture grew *Chryseobacterium indologenes* and *K pneumoniae*. The *Chryseobacterium* was only sensitive to levofloxacin and TMP-SMX on initial sensitivity reports. On DOL 42, the patient's antibiotics were changed to levofloxacin 10 mg/kg per dose every 12 hours for 14 days to treat ventilator-associated pneumonia. Additional sensitivities were requested, including ciprofloxacin to determine resistance patterns of the organism. The organism was subsequently reported be sensitive to ciprofloxacin, although no change was made because

the patient was tolerating levofloxacin. Because of a history of calcifications in the liver and spleen that were present at birth, and significant cholestasis (total bilirubin 7.1 mg/dL, direct bilirubin 3.8 mg/dL), TMP-SMX was not selected for this patient.

The patient tolerated levofloxacin well, although she did develop watery, green stools 6 days after levofloxacin was started, and this persisted for about a week after the levofloxacin was discontinued. Blood pressure and serum blood glucose remained stable throughout treatment. Complete blood counts, liver function, and renal function tests were obtained during and following the levofloxacin treatment, with no significant changes noted.

A second episode of *Chryseobacterium* ventilator-associated pneumonia on DOL 61 was treated with ceftazidime (150 mg/kg/day divided every 8 hours) when it was found to be sensitive. The patient also received vancomycin (45 mg/kg/day divided every 8 hours) because *Staphylococcus* species and *Enterococcus faecalis* were found in the urine. No further antibiotics were administered during the NICU stay. The patient was successfully extubated on DOL 65, and she was discharged home on DOL 123. No musculoskeletal issues have been identified by the pediatrician in the year since the patient received levofloxacin.

Case 4. Patient 4 was a male born via cesarean delivery at 28 weeks' gestational age with a birth weight

Table 4. Clinical Course of Neonate Described in Case 4

DOL	Culture	Organism	Sensitivity	Antibiotics
0	Blood	No growth		AMP, GEN × 2 days
4	Blood	No growth		VAN, CTX × 5 days
10	None			VAN × 1 dose (complicated PICC insertion)
13	Blood	No growth		CLX × 1 day, then VAN × 5 days
	ETT	<i>Enterobacter cloacae</i> complex	MEM, TOB, GEN, TMP-SMX	GEN × 8 days
		<i>Acinetobacter baumannii</i> complex	MEM, TOB, GEN, TMP-SMX	
17	ETT	<i>Stenotrophomonas maltophilia</i>	LVX, TMP-SMX	
		<i>Acinetobacter baumannii</i> complex	LVX, CIP, MEM, TOB, GEN, TMP-SMX	
19				LVX × 14 days
21	Blood	<i>Staphylococcus coag negative</i>	VAN	VAN × 11 days
28	ETT	<i>S maltophilia</i>	TMP-SMX	
		<i>Elizabethkingia miricola</i>	TZP, TMP-SMX	
30	ETT	<i>Pseudomonas aeruginosa</i>	MEM, CAZ, TZP, TOB, GEN	
37	Blood	No growth		GEN × 10 days
	ETT	<i>P aeruginosa</i>	Same as previous	

AMP, ampicillin; CAZ, ceftazidime; CLX, cloxacillin; CTX, cefotaxime; DOL, day of life; ETT, endotracheal tube; GEN, gentamicin; LVX, levofloxacin; MEM, meropenem; TOB, tobramycin; TMP-SMX, trimethoprim-sulfamethoxazole; TZP, piperacillin/tazobactam; VAN, vancomycin

of 1120 g. Antibiotics were administered empirically for 48 hours after birth (Table 4). On DOL 4, antibiotics (vancomycin 20 mg/kg/day divided every 12 hours and cefotaxime 100 mg/kg/day divided every 12 hours) were started for a possible sepsis and were continued for 5 days. The patient was continuously ventilated from birth and also required chest tubes. He was diagnosed with ventilator-associated pneumonia on DOL 13, with chest tubes still *in situ* and the chest X-ray showing increased density in both lungs. The white blood cell count was $41.1 \times 10^3/\mu\text{L}$ ($\times 10^9/\text{L}$), and the patient was experiencing an increase in the frequency of bradycardia and desaturation episodes. Initially cloxacillin (120 mg/kg/day divided every 8 hours) and gentamicin (2.5 mg/kg every 18 hours) were selected for treatment, the usual empiric antibiotics for late-onset sepsis at our site. However, cloxacillin was changed to vancomycin (37.5 mg/kg/day divided every 8 hours) shortly after to broaden the Gram-positive coverage because the patient continued to experience desaturations due to thick secretions which required frequent suctioning of the ETT. Levofloxacin 10 mg/kg/dose IV every 12 hours for 14 days was added on DOL 19 to treat ventilator-associated pneumonia when the repeat ETT sample grew *Stenotrophomonas* and *Acinetobacter*. Levofloxacin was selected for this patient based on organism sensitivity and the recent experience with levofloxacin for the patient described in case 3. He also received an 18-day course of dexamethasone starting on DOL 32 to facilitate extubation.

The patient tolerated levofloxacin well, although he did develop watery, green stools that continued for approximately 10 days after levofloxacin was started. Blood pressure and glucometer results remained stable throughout treatment and there were no documented cardiac concerns. Complete blood counts, liver function, and renal function tests were obtained during and following the levofloxacin treatment, and no significant changes were noted.

A repeat ETT culture grew *S maltophilia* and *Elizabethkingia miricola* on DOL 28. Because of the unusual organism that was reported and the clinical stability of the patient, the health care team decided not to modify the antibiotic coverage at that time. Sensitivity of the organisms to levofloxacin was not reported. The patient received an additional antibiotic course of gentamicin (2.5 mg/kg every 18 hours) on DOL 37 for presumed ventilator-associated pneumonia due to *P aeruginosa*. The patient was successfully extubated on DOL 45 and discharged home on DOL 125. No musculoskeletal issues have been identified by the pediatrician in the year since the patient received levofloxacin.

Case 5. Patient 5 was a male twin born at 23 + 3/7 weeks' gestational age, 470 g birth weight, intubated shortly after birth because of respiratory distress and poor tone. He was treated with 48 hours of ampicillin (100 mg/kg/day divided every 12 hours) and gentamicin (5 mg/kg × 1 dose) for suspected chorioamnionitis. On DOL 5 he was started on IV gentamicin (5 mg/kg every 48 hours), vancomycin (15 mg/kg/day given every 24

Table 5. Clinical Course of Neonate Described in Case 5

DOL	Culture	Organism	Sensitivity	Antibiotics
0				AMP × 2 days GEN × 1 dose
5	Blood	<i>Staphylococcus epidermidis</i>	VAN	FLC, GEN, VAN × 11 days
20	ETT	<i>Escherichia coli</i>	AMP, TZP, CFZ, GEN, TOB	VAN, GEN × 2 days; then AMP × 3 days
		<i>Stenotrophomonas maltophilia</i>	TMP-SMX, MIN, LVX	
		<i>Haemophilus influenzae</i>	AMP, CXM	
27	ETT	<i>S maltophilia</i>	TMP-SMX, MIN, LVX	
		<i>E coli</i>	AMP, TZP, CFZ, GEN, TOB	
		<i>Enterobacter cloacae</i>	TZP, GEN, TOB, CRO	
30				LVX × 6 days

AMP, ampicillin; CFZ, cefazolin; CRO, ceftriaxone; CXM, cefuroxime; ETT, endotracheal tube; FLC, fluconazole; GEN, gentamicin; LVX, levofloxacin; MIN, minocycline; TOB, tobramycin; TMP-SMX, trimethoprim-sulfamethoxazole; TZP, piperacillin/tazobactam; VAN, vancomycin

hours), and fluconazole (12 mg/kg load, then 6 mg/kg every 48 hours) for suspected sepsis. One of two blood cultures was positive for *Staphylococcus epidermidis*. Because of multiple clinical decompensations, the infant remained on all 3 agents for a treatment course of 11 days. During this period, a prolonged course of hydrocortisone (DOLs 15–30) was prescribed as an adjunct medication for blood pressure management.

Between DOLs 14 and 19, several attempts were made to wean ventilation, but he remained in respiratory distress. At this time, chest X-ray results showed extensive bilateral granular markings and near complete opacification of the right upper lobe. On DOL 20, vancomycin (20 mg/kg/day divided every 12 hours) and gentamicin (5 mg/kg every 48 hours) were initiated because of increasing oxygen requirements on high-frequency jet ventilation and development of hypotension. The patient did not have temperature instability or a significant change in white blood cell count, and the CRP was 11 mg/L. The differential diagnosis at this time included pulmonary embolism, pulmonary hypertension, and ventilator-associated pneumonia. Two days later ETT culture results showed moderate *Escherichia coli* and *S maltophilia*, and heavy *Haemophilus influenzae*; hence, antibiotic therapy was narrowed to ampicillin (100 mg/kg/day divided every 12 hours) for 3 additional days to decrease bacterial load in the hope of improving ventilation. The decision was made not to treat *Stenotrophomonas* because it was deemed to be colonizing the airway due to long-term intubation, and it was not ventilator-associated pneumonia causing the persistent respiratory distress.

Following a failed extubation on DOL 29, results from an ETT culture from thick, yellow secretions showed heavy *S maltophilia*, *E coli* and *E cloacae*. On DOL 30, levofloxacin 10 mg/kg IV every 12 hours was started as recommended by the infectious disease service. Twenty-four hours later, a postnatal course of dexamethasone was initiated to facilitate the next

extubation attempt. Because of the risk of corticosteroid therapy causing further immunosuppression and leading to overt ventilator-associated pneumonia, the goal was to suppress the *Stenotrophomonas* colonizing the airways during the course of steroids. The infant was successfully extubated 72 hours after the initiation of dexamethasone, and the levofloxacin course was continued for 6 days rather than the planned 10 days because of the physician's perception that the benefit of continued therapy no longer outweighed the risk. Soft, seedy, green stools were noticed on day 4 of levofloxacin therapy, but this may be attributed to the initiation of oral feeds at this time. No diarrhea or any other adverse effects were documented. Blood pressure and serum glucose values remained stable throughout treatment, and the infant had no recorded cardiac concerns. Complete blood counts, and hepatic and renal function tests were obtained during and following the levofloxacin treatment, and no significant changes were noted. The infant was discharged home on DOL 129.

Case 6. Patient 6 was a female born at 25 weeks' gestational age and with a birth weight of 590 g, was transferred from an outside hospital at DOL 86 for management of chronic lung disease, and had a difficult airway, resulting in an esophageal perforation in the first week of life (Table 6). She had multiple failed extubation attempts, including one on DOL 79. On DOL 83, an ETT aspirate grew *S maltophilia* for the first time; however, the infectious disease consultants did not feel that this was the cause of her current lung disease, and it was left untreated.

On DOL 89, the patient had increased oxygen requirements and carbon dioxide concentrations, but no temperature instability. A septic workup was completed, and the chest X-ray showed bilateral consolidation/atelectasis superimposed on chronic lung disease. Vancomycin (30 mg/kg/day divided every 12 hours) and meropenem (45 mg/kg/day divided every 8 hours)

Table 6. Clinical Course of Neonate Described in Case 6

DOL	Culture	Organism	Sensitivity
4			
50	ETT	<i>Enterococcus</i> species	AMP, VAN
62	ETT	<i>Staphylococcus aureus</i> <i>Klebsiella oxytoca</i>	OXA, ERY, CLI CFZ, CIP, GEN, TOB, PIP, TMP-SMX
83	ETT	<i>Stenotrophomonas maltophilia</i>	LVX, TMP-SMX
88	ETT	<i>S maltophilia</i> , <i>Enterobacter cloacae</i>	LVX, TMP-SMX CIP, GEN, TOB, TMP-SMX
98	ETT	<i>Stenotrophomonas maltophilia</i> <i>Chryseobacterium indologenes</i>	LVX, TMP-SMX CIP, TMP-SMX, CAZ
105	ETT	<i>S maltophilia</i> <i>C indologenes</i> Coagulase-negative <i>Staphylococcus</i>	LVX, TMP-SMX TMP-SMX Not reported
114	ETT	<i>E coli</i> <i>S maltophilia</i> <i>Pseudomonas fluorescens</i> Enterovirus /rhinovirus	AMK, MEM, ETP, TMP-SMX LVX, TMP-SMX, CAZ CIP, GEN, TOB, CAZ, TZP
117	ETT	<i>E coli</i> <i>S maltophilia</i>	AMK, MEM, ETP, TMP-SMX LVX, TMP-SMX, CAZ

AMK, amikacin; AMP, ampicillin; CAZ, ceftazidime; CFZ, cefazolin; CLI, clindamycin; DOL, day of life; ERY, erythromycin; ETP, ertapenem; ETT, endotracheal tube; GEN, gentamicin; LVX, levofloxacin; MEM, meropenem; OXA, oxacillin; PIP, piperacillin; TMP-SMX, trimethoprim-sulfamethoxazole; TOB, tobramycin; TZP, piperacillin/tazobactam; VAN, vancomycin

were started for ventilator-associated pneumonia, diagnosed based on a modified Centers for Disease Control definition. The ETT aspirate grew *S maltophilia* and *E cloacae*. In consultation with the infectious disease service, antibiotic therapy was changed to piperacillin/tazobactam (240 mg/kg/day divided every 8 hours). Shortly after, a clinical deterioration resulted in meropenem being restarted on DOL 95.

The next ETT culture on DOL 97 continued to show *S maltophilia*, and in addition grew *Chryseobacterium indologenes*. On DOL 98, the infectious disease and NICU teams elected to discontinue meropenem and treat the *Stenotrophomonas* with levofloxacin 10 mg/kg IV every 12 hours for 8 days, at which time the ETT was changed, with no obvious coating or mucus seen on the tube. Despite this treatment, on DOL 107 *Stenotrophomonas* and *Chryseobacterium* continued to be cultured from the ETT.

On DOL 116, the patient developed further signs of infection, with fever, raised oxygen requirements, and elevated CRP to 111 mg/L. The ETT cultures from that day remained positive for *Stenotrophomonas*, and this time *Pseudomonas fluorescens* and a resistant *E coli* were also cultured. Additionally, viral polymerase chain reaction test detected rhinovirus and enterovirus. She was treated with a course of vancomycin (15 mg/kg/day divided every 8 hours) and tobramycin (7.5 mg/

kg/day divided every 8 hours) for 7 days. Based on the monitoring parameters performed within the NICU (electrolytes, renal, hepatic function, serum glucose, vitals), the patient displayed no signs of adverse effects attributable to levofloxacin.

Based on the series of events and more frequent clinical deteriorations, the medical team discussed with the parents the prognosis of possible cor pulmonale and poor neurodevelopmental outcome. The recommendation to withdraw NICU support was made on the basis of medical futility and poor long-term outcome. The ETT was electively removed, and the patient died on DOL 129.

Discussion

We report 6 cases where IV levofloxacin at 10 mg/kg per dose every 12 hours was administered to treat multidrug-resistant nosocomial respiratory infections in neonates with a postmenstrual age ranging from 27 to 42 weeks, for an average duration of therapy of 10 days. In 5 of the 6 patients clinical cure occurred, although in only 2 cases was microbiologic cure demonstrated on repeat sputum culture. One patient who was not able to be extubated did not survive. Only minimal short-term adverse effects were noted. Follow-up information to assess musculoskeletal side effects within 1 year after

treatment was available for 2 cases, but longer-term follow-up for musculoskeletal or other adverse effects was not available.

Because of a lack of neonatal-specific information for levofloxacin, the usual pediatric dose was used in these cases. Levofloxacin elimination appears to be age dependent, with 87% excreted unchanged in the urine. Chien et al²⁰ found that infants and young children clear levofloxacin nearly twice as fast as adults, and therefore it is recommended that levofloxacin be administered every 12 hours. A pharmacometric analysis of levofloxacin designed to determine a dose in children for postexposure inhalational anthrax determined that a dosage of 8 mg/kg every 12 hours was appropriate for children.²¹ Although neither of these studies included infants younger than 6 months, these data formed the basis of the 12-hour dosage interval in our cases. The larger of the 2 doses recommended in these studies was selected, given the persistent nature and severity of the infections being treated and the expected larger volume of distribution in neonates. Interestingly, the pharmacokinetics of ciprofloxacin in neonates and infants younger than 3 months has recently been examined, indicating a lower clearance compared with adults and older children, with reduced dosage recommendations compared with standard references.²² This type of study is needed in order to define the optimal dosage regimen of levofloxacin for critically ill term and preterm neonates.

Levofloxacin is a bactericidal antibiotic that reaches high concentrations in the lung tissue and respiratory secretions, making it a suitable agent for the management of ventilator-associated pneumonia.²³ Many respiratory tract bacterial pathogens remain sensitive to levofloxacin, which also makes it a favorable choice in the treatment of multidrug-resistant organisms in neonates. Levofloxacin is recommended as empiric therapy for hospital-acquired pneumonia or ventilator-associated pneumonia in adults, although there are no specific antibiotic recommendations for neonates with ventilator-associated pneumonia.²⁴ Selection of empiric antibiotic therapy in the neonatal population is based on the resistance patterns identified in the specific NICU, known organism sensitivity, and known dosage and safety information in neonates. For the cases reported here, levofloxacin was selected based on reported sensitivities, persistence of organisms on previous therapy, concerns regarding adverse effects in neonates (notably kernicterus from TMP/SMX), and input from the infectious disease consultants. Because of the lack of interpretive criteria in the microbiology laboratory, *Stenotrophomonas*, which was found in 5 of these cases, is considered to be non-susceptible to ciprofloxacin.

All the neonates in the cases reported received several courses of antibiotics leading up to the infection with multidrug-resistant organisms. Prior antibiotics,

particularly third-generation cephalosporins, alter the bacterial colonization and increase the risk for nosocomial infections with multidrug-resistant organisms, morbidity, and mortality.²⁵ Tsai et al²⁶ found that multidrug-resistant bacteremia accounted for approximately 20% of bacteremia episodes in their NICU. Because empiric antibiotic regimens often do not cover these resistant organisms, the risk for severe infection and poor outcomes increases for these patients.

Although levofloxacin is typically well tolerated in both the pediatric and adult populations, one of the main concerns with its use in the critically ill neonatal patient is the unknown short- and long-term safety profile. Because of the early concerns with fluoroquinolone use in pediatric and neonatal patients, there have been no large randomized clinical trials to evaluate the efficacy and safety of these medications in this population. Most of the concerns were based on preclinical animal studies and spontaneous reports with limited objective data to confirm the findings. However, these concerns continue to limit prescribing, despite the increased experience with the use of fluoroquinolones in children.⁷⁻¹¹

Recent updates by the US Food and Drug Administration to fluoroquinolone boxed warning and drug labels associating this class of antibiotics with serious and potentially permanent side effects of the tendons, joints, muscles, nerves, and central nervous system, further promote the judicious use of these antibiotics in the pediatric and neonatal population. Noel et al²⁷ evaluated adverse effects with levofloxacin in children older than 6 months and found that although the adverse events were transient, with no severe or long-term joint abnormalities or growth impairment, there did appear to be a higher incidence of at least 1 musculoskeletal disorder (mostly arthralgia) in fluoroquinolone-treated children at 2 and 12 months after treatment compared with children treated with a non-fluoroquinolone. The American Academy of Pediatrics states that use of a fluoroquinolone in a child or adolescent may be justified in special circumstances (ie, infection is caused by a multidrug-resistant pathogen for which there is no safe and effective alternative) but makes no comment on their use in neonates.²⁸ For this reason, the use of quinolones in neonates must remain reserved for cases in which there are limited therapeutic options.

Because end points, such as arthralgia and gait abnormalities, cannot be assessed in the neonate, and objective evaluation of musculoskeletal toxicity with appropriate imaging did not occur in all study participants, extrapolation of these results to the neonatal population must be done with caution. A higher risk for arthropathies/tendon rupture has been identified when concomitant steroids are administered.²⁹ In the cases reported here, 4 neonates (cases 1, 3, 4, and 5) received steroids concomitantly with the levofloxacin. Because of the retrospective nature of this report, documentation by physician and nursing staff were relied upon to

reveal musculoskeletal toxicity, such as signs of pain when handling, visible redness or swelling of the joints, or incidental findings on imaging studies. Additionally, there is no long-term follow-up available for us to know with certainty if musculoskeletal side effects occurred in any of these patients, because some of the patients are still in prewalking stages.

Additional adverse effects should be considered when using levofloxacin in the neonatal population. In particular, the potential for QT prolongation needs to be considered if the patient has congenital long QT syndrome or is receiving any QT-prolonging medications directly or indirectly via breastmilk.³⁰ Similar to many antibiotics, the most common adverse effects of levofloxacin are gastric upset and diarrhea, which were observed in 2 of the reported cases (cases 3 and 4). Other possible adverse effects in this patient population include hepatic toxicity and dysglycemia, neither of which was observed in our patients.³¹ The unknown long-term neurodevelopmental impacts should also be considered but are challenging to quantify.

Large-scale studies would be necessary to evaluate the safety and efficacy of levofloxacin at a dosage of 10 mg/kg per dose every 12 hours. Despite an emphasis of regulatory authorities (US Food and Drug Administration and Health Canada) to improve research of drugs in pediatric patients, there remains a relative lack of data available to make informed decisions on the most appropriate dose for many medications.³²

Conclusion

Infants admitted to NICUs for prolonged periods of time are at increased risk of infections, are often exposed to repeated courses of antibiotics, and thus are more likely to develop multidrug-resistant infections. Therefore, these infants have greater need for antibiotics that are not well studied in the neonatal population. These infants represent a population in which data on the use of unconventional (at least in the NICU setting) antibiotics is needed. Clinicians often have to rely on pediatric or even adult data with regard to dosage, efficacy, and safety in these antibiotics. We report our collective experience on the use of levofloxacin in 6 neonates in 4 Canadian NICUs for the treatment of multidrug-resistant bacterial pneumonia (5 *Stenotrophomonas maltophilia*, 1 *Chryseobacterium indologenes*) using the pediatric dose of levofloxacin. Positive outcomes were achieved in 5 of the 6 patients using levofloxacin 10 mg/kg IV every 12 hours. The cases highlight the need for neonatal data on use of levofloxacin, with an emphasis on appropriate dosage and safety outcomes.

ARTICLE INFORMATION

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