

Newborn Female with Hypoxic Respiratory Failure and Persistent Pulmonary Hypertension: A Case Report

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Abstract: *Streptococcus pneumoniae* (SP) is a rare but well recognized cause of sepsis in neonates. Persistent pulmonary hypertension of newborn (PPHN) is one of the serious complications of SP and a frequent cause for morbidity and mortality in neonatal SP sepsis. It is a state of oxygenation failure characterized by high pulmonary vascular resistance with right-to-left shunting of venous blood. Inhaled NO (iNO) and extracorporeal membrane oxygenation (ECMO) have proven beneficial to infants who failed to respond to ventilation. Here we report a case of SP sepsis. The patient was a term female, who presented with rapidly progressing respiratory failure that occurred hours after birth. She subsequently developed severe PPHN, which did not respond adequately to ventilation and iNO. The patient was intermittently manually ventilated over a 3-hour period to keep SpO₂ at 50-70%. She had leukopenia, bandemia, elevated inflammatory markers, and positive blood culture for SP. Ampicillin and meropenem were administered to treat fulminant sepsis. She was transferred to a Level IV NICU in urgent need of ECMO. After transport, she improved on conventional ventilator and iNO without ECMO, and was discharged home on room air on day of life 39. The patient is currently a 12-month-old healthy female without any developmental issues.

Keywords: Neonate, sepsis, *Streptococcal pneumoniae*, pulmonary hypertension, extracorporeal membrane oxygenation.

CASE REPORT

A female infant was born by normal vaginal delivery at 39 weeks with Apgar scores of 7 at 1 minute and 8 at 5 minutes. The primigravid mother was treated for a urinary tract infection antenatally. The mother was healthy prior to the onset of labor and had no obvious signs of infection. The infant developed respiratory distress about 4-5 hours after delivery and required intubation at <12 hours of life (HOL). The infant had leukopenia (WBC = 3.4×10^3) and significant bandemia with a ratio (I/T) of immature neutrophils (band cells + myelocytes + metamyelocytes) to total neutrophils of 0.87. A blood culture sample was obtained before administering an antibiotic regime that included ampicillin, gentamicin, and cefotaxime. The neonate was transferred to the regional neonatal intensive care unit (NICU) on day of life (DOL) 2.

Upon arrival, the infant developed severe persistent pulmonary hypertension (PPHN) as

demonstrated by echocardiogram. She required intensive ventilatory support, inotropic support (dopamine and dobutamine), and a pulmonary vasodilator (inhaled nitric oxide [iNO]). Her peripheral capillary oxygen saturation (SpO₂) continued to drop to as low as 10%. She was in severe hypoxemia and respiratory acidosis with a partial pressure of oxygen (pO₂) as low as 18 mm Hg and a pH lower than 7.0 in arterial blood over a 3-hour period (Table 1, HOL 27-HOL 29.5). The oxygenation index (OI) was high at 60-70. A chest X-ray revealed moderate bilateral reticulogranularity. Surfactant therapy did not improve her hypoxic respiratory failure. Manual ventilation, with bag and mask, was more effective than mechanical ventilation in keeping SpO₂ levels between 50-70%. Transfer to a higher level NICU, equipped with extracorporeal membrane oxygenation (ECMO), was considered, but delayed, initially due to weather and later because her condition improved on DOL 3. The antibiotics regimen was changed to meropenem at the dose used to treat meningitis upon arriving at regional NICU due to severe sepsis/meningitis. Lumbar puncture was not performed because of the critical nature of the infant's condition. Inflammatory markers, including serum pro-

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Table 1: Blood Gas from Capillary (CBG) or Artery Blood (ABG) During First 2 Days of Life

	Hours of Life (HOL)	pH	pCO ₂ mm Hg	pO ₂ mm Hg	HCO ₃ mEq/L	Base Excess mEq
CBG	HOL 18	7.16	58.0		21	-8
	HOL 23	7.30	39.4		20	-6
ABG	HOL 26	7.04	66.2	18	18	-13
	HOL 27	6.97	57.6	24	13	-18
	HOL 27.5	6.98	61.2	28	14	-17
	HOL 28	6.91	82.0	26	16	-17
	HOL 29	6.92	83.3	38	17	-15
	HOL 29.5	6.95	89.3	27	20	-12
	HOL 32	7.02	75.2	30	19	-12
	HOL 35	7.19	51.9	36	20	-8
	HOL 38	7.21	51.0	37	21	-7
	HOL 39	7.26	46.8	63	21	-6
	HOL 43	7.34	40.0	91	22	-4

calcitonin (49.79 mcg/L), CRP (52.7 mg/L), and interleukin-6 (53,152.1 pg/ml) were markedly elevated. On DOL 3, blood culture results from the referral hospital (obtained prior to initiation of antibiotics) showed growth of gram-positive cocci in chains. Ampicillin (100 mg/kg/dose every 12 hours) was added to meropenem to cover Group B streptococcus (GBS) since it is the most common pathogen of neonatal sepsis. A pediatric infectious disease subspecialist was consulted, who recommended continuing the meropenem/ampicillin regimen after the pathogen was identified as penicillin-sensitive *Streptococcus pneumoniae* (SP) to make sure both GBS and SP were covered.

On DOL 6 the infant's PPHN and hypoxic respiratory distress were again aggravated. She had significant right-to-left shunting with preductal SpO₂ 20% higher than postductal. Pressure

support agents including dobutamine and dopamine were re-initiated. Inhaled NO was increased from 20 ppm to 40 ppm. In spite of the maximum ventilation with a mechanical ventilator, her postductal SpO₂ dropped to 40%. She was resuscitated using bag and mask for 30 minutes. Due to concern of uncontrolled sepsis, meropenem was discontinued. Cefotaxime and vancomycin were started at the dose used to treat meningitis to cover penicillin-resistant SP.

To make ECMO possible, the infant was airlifted to a level IV NICU. Due to improvement in oxygenation and resolution of PPHN, ECMO was not conducted. She received iNO until DOL 14, was extubated on DOL 15, reached full feeds on DOL 19, was weaned to room air on DOL 37, and discharged on DOL 39. Cerebrospinal fluid obtained on DOL 13 was within normal limits without pleocytosis. The culture of cerebrospinal

fluid was negative. Intravenous antibiotics were discontinued on DOL 21. She had a normal head ultrasound and hearing screening, and age-appropriate cognition and neurodevelopment. She had a small atrial septal defect, which did not warrant intervention.

The patient did well after discharge. Her follow-up with cardiology revealed 1/6 systolic murmur with >95% SpO₂ and no signs of residual PPHN. At her well-child visits of 2-, 4-, 6-, and 9-months, she demonstrated appropriate growth and development. She is currently 12-months-old and continues to thrive.

DISCUSSION

SP is a rare, but well recognized cause of sepsis in neonates [1-8] and is associated with significant morbidity and mortality. The clinical presentation and symptoms are non-specific and can be similar

to GBS disease. In developed countries, SP accounts for 1-11% of neonatal sepsis [2,9]. Early-onset SP sepsis is less common than late-onset SP sepsis and has a more dire prognosis, especially when it starts before 48 HOL or is secondary to an invasive maternal infection [6]. Mortality from early-onset SP sepsis was reported as 14.3% in one study and was not related to pneumococcal serogroup or susceptibilities [2]. Treatment options differ depending on penicillin sensitivity of SP. The local sensitivity pattern of SP is helpful in directing empirical antibiotic selection (Table 2).

Pneumococcal conjugate vaccine (PVC7) was introduced in 2000, and covers seven serotypes of the bacteria (4, 6B, 9V, 14, 18C, 19F, and 23F). In 2010, pneumococcal conjugate 13-valent vaccine (PCV-13) advanced the coverage to 6 additional serotypes (1, 3, 5, 6A, 7F, and 19A). The cost benefit of PCV-13 won't be seen until the

Table 2: Local Sensitivity Pattern of *Streptococcus pneumoniae* and other Pathogens in Inpatient Population of the Regional Hospital

% Sensitive Systemic Gram + Infections Cumulative Incidence at Regional Hospital	Number of Isolates	Penicillin	Oxacillin	Ampicillin	AMP/Subactam	Amox/Clavulanate	Cefazolin	Cefuroxime	Cefotaxime	Ceftioxone	Levofloxacin	Erythromycin	Tetracycline	Clindamycin	Trim/Sulfa	Vancomycin
<i>Enterococcus faecalis</i>	163	99		99							75	19	21			99
<i>Enterococcus fecium</i>	43	42		42							35	5	42			49
MSSA*	707	23	100	21	99	99	98			99	88	67	94	93	98	100
MRSA**	573										29	11	90	72	97	100
<i>Staphylococcus epidermidis</i>	242	7	28	5	28	28	28			28	57	30	86	61	61	100
Pen + <i>Streptococcus pneumoniae</i>	160	100				100		99	100	99	99	76	90	96	87	100
Pen - <i>Streptococcus pneumoniae</i>	79					91		41	92	94	95	27	51	72	46	100
Viridans <i>Streptococcus</i> group	117	61		62					93	95	89	41	70	89		100

Blank cell indicates: data are not available or drug is not appropriate for pathogen; * Methicillin Sensitive *Staphylococcus aureus*; ** Methicillin Resistant *Staphylococcus aureus*; Pen = Penicillin.

vaccinated children reach childbearing age. In our case, the mother was not vaccinated. The serotype of SP in the current case was not determined. It would be of interest to know the serotype of the pathogen that caused early onset neonatal sepsis in the era of PCV-13 [10].

The source of the infection in neonatal early-onset SP sepsis is almost invariably from the maternal birth canal, although SP is an unusual component of vaginal flora [4,9,11]. The colonization rate is extremely low ($\leq 0.03\%$) [11]. Thirty percent of mothers of infants with early-onset invasive SP infection had clinical signs of infection [12]. The invasiveness of the maternal SP infection positively correlated with the severity of neonatal disease [6]. In our case, we were told that the mother required antibiotic treatment for a postpartum febrile illness. We were unable to access the mother's medical record and did not have the details of her illness. A culture of vaginal secretions or amniotic fluid was not conducted, but could have given us more information about the source of infection.

In neonatal sepsis, endotoxin released by the pathogenic bacteria contributes to the development of PPHN, a frequent cause for NICU admission. PPHN is primarily a state of oxygenation-failure characterized by high pulmonary vascular resistance with right-to-left shunting of venous blood and is associated with right ventricle dysfunction. Surviving neonates often require prolonged cardiorespiratory support, long hospital stays, and are at high risk of long-term adverse neurodevelopmental outcomes [13]. ECMO and iNO are beneficial to infants who fail to respond to ventilation [14-16]. iNO is a selective pulmonary vasodilator that produces a rapid and sustained improvement in systemic oxygenation without excessive hypocapnia and reduces the overall need for ECMO [16].

Our patient is the first case of SP sepsis in our NICU over the past 30 years. The presentation was non-specific and akin to GBS sepsis with a very rapid progression. Her PPHN and hypoxic respiratory failure were intractable. With an OI constantly higher than 40 and poor response to ventilation or iNO, she was a candidate for ECMO. Of note, was the observation that manual ventilation with bag and mask seemed to be more effective to improve SpO₂ than mechanical

ventilation during the critical hypoxic period. The patient was intermittently manually ventilated over a 3-hour period on DOL 2 to keep SpO₂ between 50-70%. Manual ventilation by an experienced physician can easily adjust mean airway pressure and inspiratory time according to the patient's breathing. It is more flexible and can meet patient's oxygenation needs faster than mechanical ventilation. The neurodevelopment of our patient was a concern, since she had significant hypoxemia (pO₂ 18-38 mm Hg) and hypercapnia (pCO₂ 51-89 mm Hg) over an 11-hour period on DOL 2 and 3. Currently, she is 12-months-old and continues to thrive without demonstrating any cognitive or developmental issues. It is possible that avoiding hypocapnia protected her brain. Alternatively, the blood that supplied her brain was pre-ductal and might have contained a higher oxygen content.

CONCLUSION

SP is an uncommon, but well recognized cause of sepsis in newborns and should promptly be considered as part of a differential diagnosis for neonatal early-onset sepsis. ECMO should be considered in a patient with severe PPHN who does not respond to ventilation and iNO therapy.

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