Case Report

A Report on Antibiotic Management of Neonatal Sepsis Caused by *Enterobacter* spp

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Abstract

This is a report on a case of neonatal sepsis and clinical management with multiple antibiotic therapy in a neonatal intensive care unit (NICU) in Brazil. A preterm baby boy was born by caesarean section at 34 weeks and two days of gestation from an oligodramnious pregnancy with intrauterine growth restriction. After respiratory failure detection, the baby was intubated and placed on mechanical ventilation for respiratory failure and was shifted to NICU. Ampicillin and gentamicin were instituted empirically. Enterobacter spp-induced severe sepsis was diagnosed. Included in the antibiotic therapy were oxacycline, amikacin, cefepime, tazocin, meropen and teicoplanin. After sixty days in NICU, clinical and laboratory parameters were normalized and the baby recovered. The empirical long-term antibiotic treatment and the use of broad spectrum antibiotics, as observed in the present case, should be carefully considered in newborns admitted to NICU.

Keywords: Sepsis, Newborn, Respiratory failure, Multiple antibiotic therapy

INTRODUCTION

Neonatal bacterial sepsis, classified as early or late onset, is a major cause of morbidity and mortality, particularly for premature neonates, being an important public health concerns worldwide [1]. Very low birth weight infants (VLBW), weighing between 500 and 1500 g are known to have a high risk of acquiring sepsis [2], despite many advances in obstetrical and neonatal care [2]. The incidence of neonatal sepsis in developed countries ranged from 10-25 % of all infants and reached up to 50 % in VLBW infants [1]. Neonatal infections are considered infections derived either intrapartum from the mother's flora, or acquired in the hospital

[3].Early onset neonatal sepsis (EOS) occurs in the first three days of life, which is typically caused by organisms transmitted vertically from the mother to the infant before or at the time of birth [4]; while late onset neonatal sepsis (LOS), an infection occurring after day 3 of life, is more likely to be caused by pathogens acquired during the course of hospital care. Besides higher risk of mortality caused by neonatal sepsis, survivors of neonatal sepsis may develop severe morbidity secondary to concomitant meningitis or from hypoxemia resulting from persistent pulmonary hypertension, septic shock, and respiratory failure [5]. Early onset neonatal sepsis (EOS) is reported to be caused primarily by *Streptococcus agalactiae* and *Escherichia coli* in high income

countries [6]. In developing countries, bacteria like *Klebsiella* spp., *Escherichia coli*, and *Staphylococcus aureus* are reported to be the main cause reason of neonatal sepsis within the first week of life [7]. The spectrum of bacteria seen in early onset newborn sepsis also depends on the gestational week [8]. In mothers who received intrapartum or prepartum antibiotic treatment, there is likelihood to encounter infections with *Enterobacter* or *Klebsiella* spp. [5]. In recent years, the incidence of infections with Gram-negative rods such as *Escherichia coli*, *Enterobacter* spp, and *Klebsiella* spp seemed to increase in many neonatal intensive care unit (NICU) worldwide [5].

Enterobacteriaceae was noted to pose an increasing problem in the recent years, causing severe nosocomial infections. Besides rapid diagnosis, the immediate initiation of treatment is of great importance for a favorable treatment outcome. Suspected infections are quite frequent in premature newborns and empirical antibiotic therapy is an emergency. If treatment is delayed or ineffective, neonatal sepsis can be rapidly fatal, making optimal use of antibiotics is most essential. Empiric antibiotic therapy in newborns is based on combinations of cephalosporin, ampicillin and gentamicin [9,10]. A prolonged empiric antibiotic therapy after birth, however, was shown to be problematic in pre-term infants. Thus, either toxic or subtherapeutic treatment courses may exist in the neonatal clinical care, promoting adverse reactions and antibiotic resistance which obviously impacts clinical outcomes.

We report a clinical course of antibiotic therapy occurred in a NICU from Brazil.

CASE REPORT

A preterm baby boy with birth weight of 2.14 kg was by caesarean delivery at 34 weeks and two days of gestation at a public hospital, in a city of Paraná State, Brazil, in April 2014. The oligodramnious pregnancy of twins was diagnosed with intrauterine growth restriction and presence of grade II placenta. One of the twins died after caesarean. The surviving infant was well at birth, with Apgar scores of 8 and 10, at 1 and 5 min, respectively. The temperature was 36.50 °C, heart rate 134-138/min, respiratory rate 36-46/min, perfusion < 3 s. Since the respiratory course deteriorated with worsening saturation, the baby was intubated and placed on mechanical ventilation for respiratory failure. On the second day of birth, the infant presented with

jaundice and respiratory failure and was shifted to NICU. The symptoms were suggestive respiratory distress syndrome (RDS) or pulmonary infection. The hematological parameters and blood culture were investigated. Ampicillin (200 mg,i.v.,12 h) and gentamicin (9 mg, i.v., 36 h) were instituted empirically. Cardiovascular drugs, such as dobutamine (6 mg/kg/min), and opioid (fentanyl, 2 mg/kg/min) were administered and secondary hypertensive state was observed. At 6th day in the NICU, hypoglycemia was observed and thrombocytopenia was not elicited (136,000 × 10^9 platelets/L). Dexamethasone (0.3mg, i.v.,6 h) was also introduced to avoid broncopulmonary dysplasia. At 9th day, the results of blood culture were not yet available, bradycardia was detected and antibiotic therapy was changed to oxacilin (50 mg, i.v., 12 h) and amikacin (28 mg, i.v., 24 h), suggesting low efficacy of gentamicin and ampicillin combination and urine culture was negative. In the following days, bradycardia was restored by dobutamine administration. The antibiotic cefepime (93 mg, i.v., 12 h) was also included in the treatment. The investigations revealed leukocytosis, thrombocytopenia (26,000 × 10^9 platelets/L) and C-reactive protein. Platelet transfusion was required. On 15th day blood culture yielded, *Enterobacter* spp, confirming the diagnosis of severe sepsis. Tazocin (180 mg, 8 h) was immediately administrated.

Two days after, pneumoperitoneum was observed and thrombocytopenia was continuous (32,000 × 10^9 platelets/L). The appendix was determined as perfored and obstructed and appendectomy was performed. Severe alterations in haemogram and C-reactive protein were observed and in the antibiotic therapy were included meropenem (40 mg, i.v., 8 h) and teicocloplanin (20 mg; i.v., 12 h). As the clinical state worsened, vancomycine (30 mg, i.v., 8 h) and mycamine (20 mg, i.v., 24 h) were introduced, but it caused seizure state and ascite formation. Furosemide (20 mg, i.v., 12 h) was recommended, since oliguria and hypervolemia were presented. At this stage platelet level was 8.000 × 10^9 platelets/L, with continuous antibiotic therapy. Since many drugs were used in this clinical case, drug–drug interaction was possible. However, using the Naranjo Adverse Drug Reaction Probability Scale, it was observed that a "possible adverse drug reaction" (score 4), related to a continuous thrombocytopenia.From 30th and following days, clinical and laboratory parameters were normalized. One month after discharge from NICU, the infant was in good general condition.

Data collection was done retrospectively on the basis of medical records. Newborn sepsis was defined as acquiring a sepsis within 30 days after birth. Early onset sepsis was defined as having a positive blood culture within 72 h and late onset sepsis after 72 h of delivery. Additionally, diagnosis of sepsis was based on having at least two clinical signs of sepsis (core temperature > 38.5 °C, tachycardia/bradycardia or tachypnea) and one positive laboratory parameter linked to sepsis, i.e., white blood cell count and a C-reactive protein (CRP).

Ethical approval

This report was approved (approval nº 919.213-COPEP/UEM) by Ethics Committee of State University of Maringá, Brazil.

DISCUSSION

Early onset neonatal sepsis was reported within the first week of life. Many factors are involved in the onset of sepsis, including: gestational age, caesarean or spontaneous vertex delivery, Apgar score and infant weight. Gram negative bacteria such as *Enterobacter* spp played an important role in neonatal sepsis in NICUs [5-7] predominantly in premature newborns with VLBW (below 2,500 g) and in one-third of cases, it was related to surgical interventions or previous antibiotic therapy during pregnancy period [12].

As microbiologically evaluated infection is rare in neonates, treatment has to be started as early as possible and merely upon clinical suspicion. Indeed, faster and specific tests are necessary to avoid the inappropriate use of antibiotics, since it has been reported multiresistant bacterial strain. Failure to recognize that resistant strains may result in ineffective antibiotic therapy with its attendant morbidity and mortality.

The initial choice of antibiotic therapy will depend on the clinical context and local bacterial epidemiology. In all cases, newborns who acquired an infection with Enterobacteriaceaeare empirically treated with ampicillin, gentamicin and/or cephalosporin before the onset of the sepsis. In this context, prolonged (> 5 days) empirical treatment/prophylaxis with broad spectrum antibiotics was shown to be associated with a higher risk of late onset sepsis (LOS), necrotizing enterocolitis and mortality in preterm infants [11,12]. In this study, it was observed that the mean duration of empirical antibiotic treatment was 7 days. This is noteworthy in view of the high resistance and mortality rates often

seen in newborns with LOS due to failure of empirical treatment. We can only speculate that some resistance was caused by strain selection due to long-term initial antibiotic therapy or passed on to the newborns via their mothers around birth. The present case is early onset sepsis and the baby could have acquired from the mother. At the moment it is not possible to give a concluding statement on this question.

The possibility of a nosocomial infections outbreak of multi-resistant strains is argued against by the fact that there was no timely gathering of cases. Here, we are furthermore limited by the fact that we are not able to provide data about various bacterial strains involved in this case. Indeed, the treatment of neonatal sepsis is a challenge. The neonate had immunosuppression or debilitation because of prematurity, respiratory tract instrumentation, NICU stay and use of broad spectrum antibiotics. The treatment needs to be rapid, appropriate for the pathogen and safety of the neonate. The challenge seems to be increasing with each passing day due the escalating multidrug-resistant organisms [9]. In practice, ampicillin or amoxicillin in combination with an aminoglycoside (amikacin or gentamicin) is the most common antibiotic regimen for neonatal sepsis.

The use of many classes of antibiotics clearly demonstrated a possible resistance of bacteria involved in sepsis. In fact, the use of broad spectrum antibiotics in the present case may have resulted in antibiotic selection pressure on the bowel inhabitants resulting in increased survival and overgrowth of the resistant population. In case of severe infection due to multidrug-resistant members of the Enterobacteriaceae, including those with extended-spectrum β-lactamases (ESBLs) or AmpCs, carbapenems and quinolones are used as the last resort for treatment [12].The choice of antibiotics should also be based on susceptibility reports, type of infection being treated, the severity of the infection and clinical response to the regimen chosen.

CONCLUSION

The empiric long term antibiotic treatment and the high number of late onset sepsis with often multiresistant Enterobacteriaceae might be causal and urges for a change in general antibiotic prophylaxis/treatment in newborns admitted to the NICU. As described in this case report, the findings demonstrate the need for strict enforcement of infection control practices, whereas an early microbiology screening plays a

pivotal role in early detection and reporting of antibiotic resistance. In addition, close liaison between the clinicians and the microbiologists will facilitate a significant reduction in morbidity and mortality in NICU. The emergence and spread of these pathogens can be significantly curtailed if appropriate infection control procedures, strict enforcement of antibiotic policies and screening programs are implemented immediately.

ACKNOWLEDGEMENT

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