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Case Report

Treatment of Infection Caused by Vancomycin-Resistant *Enterococci* in Extremely Preterm Neonate

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Abstract

Background: *Enterococci* are facultative anaerobic microorganisms and opportunistic pathogens. Risk factors for enterococcal infection in neonates are prematurity, low birth weight, long-term hospitalization in the neonatal intensive care unit, immaturity of the innate and adaptive immune response, mechanical ventilation and other invasive procedures. Vancomycin-resistant *Enterococci* has increased significantly over the last two decades as important cause of nosocomial infections.

Case description: The preterm male neonate was born by vaginal delivery at $25^{5/7}$ weeks of gestation with birth weight of 900 g and Apgar score of 2 in the first minute after birth. After initial stabilization in Maternity Hospital, the neonate was admitted to the Institute of Neonatology on the 3rd day of life in severe condition. On the 28th day of life, the neonate developed signs of systemic infection. Complete blood count showed leukocytes of 6300/mm^3 and increased concentration of C-reactive protein (90.2 mg/L). Analysis of cerebrospinal fluid obtained by lumbar and ventricular puncture showed pleocytosis, hyperproteinorachia and hypoglycorrhachia. We received a positive result of the tracheal aspirate for *Enterococcus faecalis* with sensitivity only on linezolid. Because of that, we added linezolid in the therapy. However, *Enterococcus faecium* grew in the blood and cerebrospinal fluid. In accordance to the antibiogram, the antibiotic therapy was replaced to chloramphenicol. Head ultrasound showed posthemorrhagic ventricular dilatation, increased thickness, irregularity and echogenicity of the ependyma, the presence of intraventricular debris and stranding and fibrin sept formation in left lateral ventricle. During treatment by chloramphenicol the neonate had a mild gray skin color, but count of blood cells, and function of liver and kidneys were normal. After the completion of treatment of neonatal sepsis complicated by meningitis and ventriculitis, ventriculoperitoneal shunt implantation was performed.

Conclusion: There is a need for implementation of strategies for control of colonization by vancomycin-resistant *Enterococci* in pregnant women, as wells as preventive measures in daily work and rational use of antibiotics in the neonatal intensive care unit. Chloramphenicol could be used as a new treatment option for neonatal sepsis caused by vancomycin-resistant *Enterococci*, especially associated with infection of central nervous system with monitoring complete blood count, liver and kidney function of the neonate.

Keywords: *Neonatal Sepsis, Neonatal Meningitis, Ventriculitis, Vancomycin-Resistant Enterococci, Preterm Neonate*

Introduction

Gram-positive bacteria of the genus *Enterococcus* are facultative anaerobic microorganisms and opportunistic pathogens. There are two the most common *species in humans, Enterococcus faecalis and Enterococcus faecium*. Although *Enterococci* are among the first bacteria that colonize the gastrointestinal tract of the neonates, these bacteria can cause early-onset sepsis (EOS) and late-onset sepsis (LOS), especially in preterm neonates, which is related to long-term hospitalization in the neonatal intensive care unit (NICU) and immaturity of the innate and adaptive immune response. Also, these neonates need for variety invasive procedures, such as endotracehal intubation, mechanical ventilation (MV), lumbar puncture (LP), which increases the risk of infection. Thanks to the ability to survive in unfavorable conditions and the rapid development of resistance to antibiotics, *Enterococci* persist for a long time on various surfaces and objects in the nosocomial environment, as well as on the hands of healthcare workers. (1,2) Vancomycin-resistant *Enterococci* (VRE) were first reported in humans in England in 1988. The prevalence of infections caused by VRE has increased significantly over the last two decades and is among the three most important microorganisms that cause nosocomial infections. However, data on outbreaks and individual cases of VRE infection in NICU are scarce. (2-5) Thus, we present our challenges of the treatment LOS complicated with meningitis and ventriculitis caused by vancomycin-resistant *Enterococci*.

Case Presentation

The preterm male neonate with birth weight of 900 g was born by vaginal delivery at $25^{5/7}$ weeks of gestation from primigravida. The Apgar score was 2 at first minute after birth. The mother was diagnosed with vaginal bleeding, as well as elevated concentration of C-reactive protein (CRP) on admission in Maternity Hospital (MH). Immediately after birth, the neonate was intubated and shifted to NICU, where the neonate was placed on conventional MV and surfactant was administered. Also, the neonate was started on empirical antibiotic therapy (ampicillin and gentamicin), prophylactic doses of fluconazole, caffeine for stimulation of breathing and total parenteral nutrition.

After initial stabilization in MH, the neonate was admitted to NICU in the Institute of Neonatology on the 3rd day of life (DOL), in severe condition, orotracheally intubated, with a weight of 810 g and normal vital signs. After admission in our NICU, conventional MV and therapy started in MH were continued. The neonate had clinical and echocardiographic signs of hemodynamic significant patent ductus arteriosus, so ibuprofen intravenously (i.v.) was used to close it. The head ultrasound (HUS) showed moderate echogenicity of the brain parenchyma in the periventricular region and grade II of intraventricular hemorrhage (IVH). Because of neonatal seizures, the neonate received phenobarbital. During the control HUS, a further increase in the volume of IVH (grade III) and the size of the lateral ventricles were shown. A neurosurgeon was consulted, serial removal a small amount of cerebrospinal fluid (CSF) by LP were performed daily.

On the 28th DOL, the neonate developed signs of systemic infection, such as respiratory distress, marbled skin, hypotonia, and distention of the abdomen followed by feeding intolerance. Complete blood count (CBC) showed leukocytes of 6300/mm^3 with 51% neutrophils and 39% lymphocytes, normal count of platelets (342.000/mm^3), low concentration of hemoglobin (93 g/L) and increased concentration of CRP (90.2 mg/L). Cytologic and biochemical examination of CSF obtained by LP showed pleocytosis, hyperproteinorachia and hypoglycorrhachia. Chest radiography showed bilateral pneumonia. After the neonate's blood, CSF and tracheal aspirate sent for culture, dual antibiotic therapy (meropenem 40 mg/kg/dose i.v. and vancomycin 15 mg/kg/dose i.v.) with prophylactic doses of fluconazole was started. First of all, we received a positive result of the tracheal aspirate for *Enterococcus faecalis* with sensitivity only on linezolid (Table 1.). Because of that, we added linezolid (10 mg/kg/dose i.v.) to the therapy. However, *Enterococcus faecium* grew in the blood and CSF (Tables 2. and 3.). In accordance with the antibiogram, the antibiotic therapy was changed to chloramphenicol (25 mg/kg/dose i.v.).

Table 1. Tracheal aspirate culture with antibiogram.

Positive: ***Enterococcus faecalis***			
Ampicilin	R	Imipenem	R
Cefalosporins	R	Vancomycin	R
Teicoplanin	R	Linezolid	S

R – resistant, S – sensitive

Table 2. Blood culture with antibiogram.

Positive: ***Enterococcus faecium***			
Ampicilin	R	Imipenem	R
Cefalosporins	R	Chloramphenicol	S
Gentamicin (high doses)	R	Streptomicin (high doses)	S
Vancomycin	R	Teicoplanin	R
Linezolid	S		

R – resistant, S – sensitive

Table 3. Cerebrospinal fluid culture with antibiogram.

Positive: ***Enterococcus faecium***			
Ampicilin	R	Imipenem	R
Cefalosporins	R	Chloramphenicol	S
Gentamicin (high doses)	R	Streptomicin (high doses)	S
Vancomycin	R	Teicoplanin	R
Linezolid	S		

R – resistant, S – sensitive

The neonate had an increase in head circumference associated with a moderate bulging of anterior fontanelle. During HUS follow-up, further increase in the size of the lateral ventricles was observed. Also, increased thickness, irregularity and echogenicity of the ependyma, the presence of intraventricular debris and stranding and fibrin sept formation in left lateral ventricle were shown (Figure 1). This HUS findings highly suggestive associated with ventriculitis. Ventricular puncture was performed by a neurosurgeon and CSF analysis showed pleocytosis, hyperproteinorachia and hypoglycorrhachia. Due to very low body weight and the presence of intracranial infection, there was a contraindication for the placement of a ventriculoperitoneal (VP) shunt.

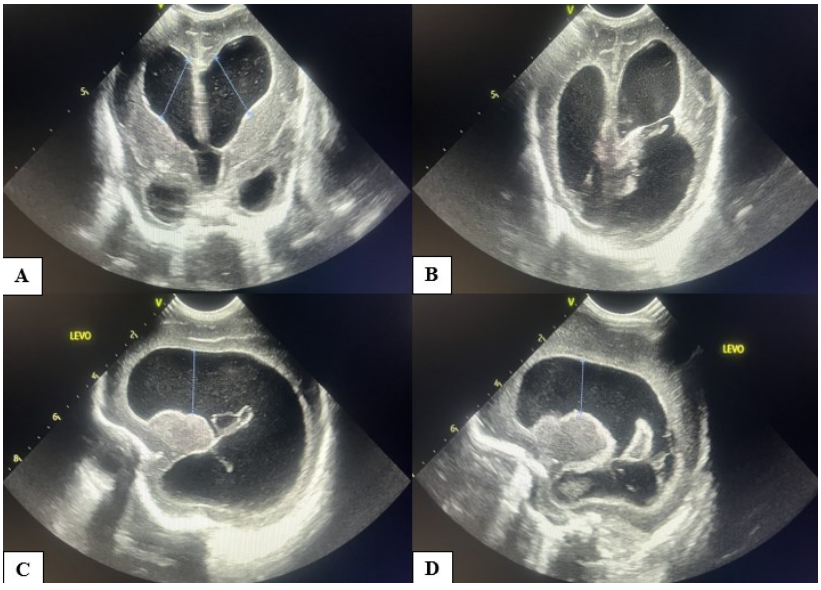

Figure 1. *Head ultrasound showed posthemorrhagic ventricular dilatation, the presence of intraventricular debris and stranding in lateral ventricles, with fibrin sept formation in left lateral ventricle. A and B: coronal images, C and D: sagittal images.*

During treatment by chloramphenicol the neonate had a mild gray skin color. A gradual decrease in CRP concentration is registered. The count of granulocytes, erythrocytes and platelets were within normal ranges, as well as serum biochemistry analysis (concentrations of urea, creatinine, total protein, albumin, activity of aspartate aminotransferase (AST), alanine aminotransferase (ALT), γ-glutamyl transferase (γ-GT), concentrations of total and direct bilirubin). Abdominal ultrasound showed normal finding. No VRE was isolated from neonate on a repeat blood and CSF culture.

After the completion of treatment of LOS complicated by meningitis and ventriculitis, neurosurgical treatment of posthemorrhagic ventricular dilatation (PHVD), VP shunt implantation was performed.

Discussions

During the last few decades, advances in neonatal intensive therapy and care, such as the use of MV and various modes of noninvasive ventilation, the use of surfactants and antenatal corticosteroid therapy in order to mature of the fetal lung, contribute to increased survival of preterm neonates. Neonatal sepsis is a significant cause of morbidity and mortality in preterm and low birth weight neonates. (1,6) Our patient was extremely preterm neonate, which required endotracheal intubation, the use of MV and hospitalization in the NICU immediately after birth. Also, this neonate received several different antibiotics during the first month of life, and due to PHVD repeated LPs were performed daily. All of these are well-known risk factors for developing neonatal LOS.

Over time, *Enterococci* has evolved from harmless intestinal commensals to a significant cause of nosocomial infection. In addition to LOS, enterococcal infection can occur in the first 72 hours after birth, as EOS, through vertical transmission of bacteria from the infected birth canal of the mother to neonate. (1,3) *Enterococci* are very resistant bacteria to common antiseptics and disinfectants; they can survive for a very long time on the objects in hospital and on the hands of healthcare workers. The risk of serious enterococcal infections is associated with previous antibiotic exposure disrupting normal gut microbiomes. It is resulting intestinal wall translocation of bacteria and transportation to the lymphatic system, where bacteria come into contact with the cells of the immature immune system of the preterm neonates, which allows the infection to spread. (7) *Enterococci* have intrinsic resistance to various antibiotics, such as penicillin's, cephalosporins, clindamycin, aminoglycosides and trimethoprim-sulfamethoxazole. In the last three decades, particularly virulent strains of multidrug-resistant (MDR) *Enterococci*, especially VRE, have appeared. Due to the survival in unfavorable conditions of *Enterococci* in the external environment and resistance to a large number of antibiotics, the treatment of enterococcal infections represents a great challenge at any age, especially in neonates. (3,7,8)

The only antibiotic approved by the Food and Drug Administration for the treatment of VRE infection is linezolid. Other antibiotics that can be used in therapy are daptomycin and quinupristin/dalfopristin, but the use of quinupristin/ dalfopristin is limited because of its adverse effects profile. In addition, as a last option, the so-called "salvage therapy" in the treatment of VRE infection is tigecycline. (7) Hapnes et al. (9), showed a case report of persistent bacteremia caused by vancomycin and high-level gentamicin resistance *Enterococcus faecium* in a 10-day-old extremely preterm male neonate who was successfully treated with linezolid. Our patient had sepsis complicated with pneumonia and infection of central nervous system (CNS). Based on the isolate and the antibiogram of the tracheal aspirate culture, the initial treatment was started with linezolid. However, five days later we got analysis of blood and CSF culture. *Enterococcus faecium* was isolated with sensitivity only on linezolid, chloramphenicol and high doses of streptomycin. Since linezolid is not recommended in pediatric patients with CNS infections due to variable concentrations of linezolid in CSF, we started chloramphenicol. Chloramphenicol easily penetrate through the blood-brain barrier (BBB) and is recommended as a reserve antibiotic for patients with allergies to beta-lactam antibiotics or CNS infections caused by MDR bacteria. (10,11)

Chloramphenicol was discovered in 1947, but twelve years after that the first case report of a potentially fatal adverse reaction in a neonate was published. Due to the gray color of the neonate's skin, this adverse reaction to chloramphenicol is named gray-baby syndrome and is characterized by abdominal distention, vomiting, hypothermia, cyanosis and hemodynamic instability. The immature liver of the neonate cannot completely metabolize chloramphenicol via the enzyme UDP-glucuronyl transferase. Similarly, the neonatal kidneys are unable to excrete chloramphenicol, which increases the concentration of chloramphenicol in the blood.

Chloramphenicol has a direct effect on electron transport within the respiratory chain in mitochondria, disrupting oxidative phosphorylation and energy synthesis in cells. Also, in the blood, chloramphenicol displaces indirect bilirubin from albumin molecule, which increases its concentration and the risk of the bilirubin-induced neurologic dysfunction. (12) Although preterm neonates are at the highest risk of developing gray baby syndrome, in our extremely preterm neonate, apart from the mild gray color of the skin, the biochemical parameters for the assessment of liver and kidney function were in the normal ranges.

The use of chloramphenicol is associated with the occurrence of an idiosyncratic reaction in the form of aplastic anemia, which is irreversible and occurs rarely. In addition, serious bicytopenia and pancytopenia (hypoplastic anemia, thrombocytopenia, granulocytopenia) are possible due to reversible bone marrow suppression, which is dose-dependent. Blood dyscrasias have occurred both after short-term and prolonged therapy with chloramphenicol. (10) Because of that, in our patient, we often controlled CBC, but there were no abnormalities in the count of blood cells.

There is no literature data about the use of chloramphenicol in the treatment of infection caused by VRE, especially in preterm neonates. However, we successfully used chloramphenicol in the treatment of infection caused by VRE in extremely preterm neonate with adequate monitoring of the occurrence of potential side effects of the drug.

Conclusion

There is a need for implementation of strategies for control of colonization by VRE in pregnant women. It is necessary to implement adequate preventive measures in daily work in the NICU, such as hand hygiene of healthcare workers, use of automated mobile ultraviolet devices without contact and routine cleaning of surfaces with chlorhexidine. The rational use of antibiotics plays a significant role in preventing the appearance and spread of these bacteria. In case of neonatal sepsis, especially associated with CNS infection caused by VRE, chloramphenicol can be used as a new treatment option with frequent monitoring of CBC, liver and kidney function.

Conflict of Interest

The authors declare no conflict of interest.

Acknowledgement

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