Neonatal Sepsis by Bacteria: A Big Problem for Children

Emma Saez-Lopez, Elisabet Guiral and Sara M Soto*
Barcelona Centre for International Health Research (CRESIB, Hospital Clinic-University of Barcelona), Barcelona, Spain

Introduction

Neonatal sepsis is an important but underestimated problem around the world. It is defined as disease affecting newborns ≤ 1 month of age with clinical symptoms and positive blood cultures. Infection is an important cause of morbidity and mortality during the neonatal period, despite the great improvements in intensive neonatal care and the use of extended spectrum antimicrobial agents. The incidence of this disease in developed countries is 1/1,000 in normal term neonates and 4/1,000 in preterm neonates. These values increase in low-weight preterm neonates [1]. In developing countries, this incidence increases to 2.2-8.6/1,000 live births [2]. Neonatal sepsis can be subdivided into early-onset neonatal sepsis and late-onset neonatal sepsis.

Early Onset Neonatal Sepsis

EONS can be acquired vertically from the pregnant woman before or during delivery. In this case, microorganisms present in the genital tract of the mothers are of great importance [3]. The symptoms appear within the 72 hours of life. EONS is a serious problem among very-low-birth-weight (VLBW) neonates and is associated with at least a three-fold increased risk of mortality [4]. The estimated incidence in this group is about 15-19/1000 live births [5].

Among the risk factors associated with EONS, the duration of gestation at delivery and the presence of maternal genital tract infection are the most common. In the case of early neonatal sepsis caused by bacteria, these microorganisms could arise from a prematurely ruptured amniotic membrane which becomes infected generally affecting the amniotic fluid or preterm delivery in a mother colonized by such bacteria and who may have a much higher risk of infecting their offspring due to the immaturity of their immune system [6,7]. The intraamniotic infection can affect maternal tissues such as decidua and myometrium, and also fetal tissues such as amniotic and chorionic membranes (choioamnionitis), amniotic liquid (amnionitis), umbilical cord (funisitis) and placenta (villitis) [8]. The microorganisms can arrive to the amniotic cavity through the blood system of the placenta, by invasive procedures during gestation (amnioncensis, etc) and by an ascending pathway [9].

Ascending infection from the genital tract of the mother to the fetus requires the following steps [9]:

I- Presence of bacteria in the vagina/cervix.

II- Bacteria residing in the decidua.

III- The bacteria might colonize the amnion or the chorion, going through the fetal vessels or crossing the amnion, reaching the amniotic cavity.

IV- The bacteria enter the fetus through contact with the infected amniotic liquid and reach the blood, causing sepsis.

Intrauterine or congenital transmission through the placenta affecting the fetus during pregnancy should be differentiated from perinatal transmission, which takes place at delivery and is caused by contact with the microbiota of the birth canal and perineal area.

The main vertically transmitted microorganisms causing EONS are Streptococcus agalactiae (or group B Streptococcus GBS) and Escherichia coli, followed by Coagulase-negative Staphylococcus (CONS), Haemophylus influenza and Listeria monocytogenes [3]. These microorganisms are an important source of problems for the health of neonates worldwide.

Several studies have corroborated this etiological data. Stoll et al. [10] found that 44% and 10.7% of EONS were caused by E. coli and SGB, respectively. Among EONS cases Vergnano et al. [11] reported that 50% were caused by SGB and 18% by E. coli, this last microorganism being more frequent among very low birth-weight (VLBW) neonates. Other studies are compiled in Table 1 [12-18].

Dagnew et al. [19] carried out a review of the studies about the frequency of GBS causing EONS in developing countries. The incidence rate of 0-2.06 per 1,000 live births and the prevalence of other microorganisms causing EONS varied within and between geographic regions. In Arabic countries, Gram-negative microorganisms are more frequently found as cause of EONS than Gram-positive microorganisms [20]. Finally, Klebsiella spp. (from blood samples) and Staphylococcus aureus (from pus swabs samples) were the bacteria more frequently involved in EONS in Tanzania [21].

Late Onset Neonatal Sepsis

LONS occurs at 4-90 days of life and is acquired from the care giving environment [22]. The incidence ranges from 1.87 to 5.42 per 1,000 live births [11]. The microorganisms most frequently found to cause LONS are CONS, Staphylococcus aureus, E. coli, Klebsiella,

Table 1: Frequencies of GBS and E. coli described in several studies on EONS

<table>
<thead>
<tr>
<th>Reference</th>
<th>Geographical area</th>
<th>Period</th>
<th>GBS</th>
<th>E.coli</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brzaro et al. (2005) [12]</td>
<td>Yale (USA)</td>
<td>1989-2003</td>
<td>49%</td>
<td>24%</td>
</tr>
<tr>
<td>Coben-Wolanez et al. (2009) [13]</td>
<td>USA</td>
<td>1996-2007</td>
<td>0.65/1,000</td>
<td>0.2%</td>
</tr>
<tr>
<td>Van den hoggen et al. (2010) [14]</td>
<td>Netherlands</td>
<td>2003-2006</td>
<td>0.7%</td>
<td>18%</td>
</tr>
<tr>
<td>Sgro et al. (2011) [16]</td>
<td>Canada</td>
<td>2006-2008</td>
<td>163%</td>
<td>264%</td>
</tr>
<tr>
<td>Stoll et al. (2011) [17]</td>
<td>USA</td>
<td>2006-2009</td>
<td>43%</td>
<td>29%</td>
</tr>
<tr>
<td>Weston et al. (2011) [18]</td>
<td>USA</td>
<td>2005-2008</td>
<td>38%</td>
<td>24%</td>
</tr>
</tbody>
</table>

*Corresponding author: Sara M. Soto, Barcelona Centre for International Health Research (CRESIB, Hospital Clinic-University of Barcelona), Barcelona, Spain, Tel: +34-932275707; E-mail: ssoto@clinic.ub.es; sara.soto@cresib.cat

Received July 26, 2013; Accepted August 14, 2013; Published August 16, 2013


Copyright: © 2013 Saez-Lopez E, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.
The empirical treatment of EONS consists of antibiotics effective against the most likely pathogens such as GBS, Gram-negative bacteria and Listeria and have synergic action. The combination of ampicillin - cefotaxime is only given in the case of meningitis determined by CSF positivity or by clinical suspicion. In the case of LONS, the therapy must be of extended spectrum antibiotics in order to cover Gram-negative and Gram-positive microorganisms. The duration of antibiotic therapy is of 10 days in EONS without meningitis, 10-14 days in LONS without meningitis, and 14-22 days in the cases of neonatal meningitis. However, an increase in the percentage of Gram-negative bacteria resistant to Am and Gm has been observed [24, 33, 34]. Several studies found that the 75-78% of E. coli strains causing EONS were ampicillin-resistant and 19-53% were gentamicin-resistant [24, 33]. In the case of E. coli isolates from LONS, between 19-50% were ampicillin-resistant and 9-16% were gentamicin-resistant [24, 33]. This trend has also been observed in developing countries [35]. For these reasons, although the current guidelines for empirical therapy in neonates seem to be appropriate [32], it is necessary to carry out studies about the susceptibility of bacteria causing neonatal sepsis in order to avoid an emergence and/or an increase in resistance levels. After empirical treatment, the choice of the antibiotics depends on the microorganism isolated, their antimicrobial susceptibility and the mechanisms of resistance used by the microorganism.

**CDC Prophylaxis Guidelines**

*Streptococcus agalactiae* or group B *Streptococcus* (GBS) has been the main etiologic agent of early neonatal sepsis in developed countries. In developing countries, this remains to be confirmed, although the few reports available point out that GBS is also a highly prevalent cause of neonatal infections. This microorganism belongs to the gastrointestinal tract microbiota from where it can colonize the vagina. Colonization of a pregnant woman's vagina is very important, as it implies an enhanced risk of GBS being transmitted vertically to the child before or at birth, and subsequently causing infection in the newborn. In Spain, it has been reported that 10-18.5% of pregnant women are colonized by GBS [36, 37]; 22.76% in Tehran [37]; 6% in Iran [38]; 19% in Poland [39]; and 20% in Taiwan [40]. To avoid this enhanced risk of vertical transmission, several diagnostic and prophylactic protocols have been proposed. In 1996, the Center of Disease Control (CDC) recommended taking vaginal and rectal samples from pregnant women in their last antenatal visit and administering a prophylactic antibiotic such as penicillin G or ampicillin during pregnancy or at the time of delivery in women found to be colonized by GBS in antenatal screenings. If the pregnant woman is allergic to betalactamics, erythromycin or clindamycin must be used [41]. When implemented, the use of these prophylactic measures resulted in a decrease in the incidence of infection by GBS. A good example of this success was a study carried out in 10 hospitals of Barcelona (Spain) in which it was found that the incidence of GBS as cause of neonatal sepsis was reduced from 1.92/1,000 newborns in 1994 to 0.26/1,000 newborns in 2001 (p < 0.001) [42]. Another study revealed a decrease in the incidence of GBS vertically transmitted.

### Table 2: Studies about etiology of LONS

<table>
<thead>
<tr>
<th>Reference</th>
<th>Geographical area</th>
<th>Period</th>
<th>GBS</th>
<th>E.coli</th>
<th>S. aureus</th>
<th>CONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bizzar et al. [12]</td>
<td>Yale (USA)</td>
<td>1989-2003</td>
<td>4%</td>
<td>10%</td>
<td>7%</td>
<td>43%</td>
</tr>
<tr>
<td>Cohen-Wolkowicz et al. [15]</td>
<td>USA</td>
<td>1996-2007</td>
<td>0.24/1,000</td>
<td>0.61/1,000</td>
<td>1.01/1,000</td>
<td>1.22/1,000</td>
</tr>
<tr>
<td>Vergano et al. [14]</td>
<td>England</td>
<td>2006-2008</td>
<td>8%</td>
<td>13%</td>
<td>18%</td>
<td>54%</td>
</tr>
<tr>
<td>Waters et al. [23]</td>
<td>Low &amp; middle income countries</td>
<td>1980-2010</td>
<td>2.4%</td>
<td>12.2%</td>
<td>14.9%</td>
<td></td>
</tr>
<tr>
<td>Hammoud et al. [26]</td>
<td>Kuwait</td>
<td>2005-2009</td>
<td>0.3%</td>
<td>5.8%</td>
<td>1.7%</td>
<td>35.5%</td>
</tr>
<tr>
<td>Didier C et al. [25]</td>
<td>Alsace (France)</td>
<td>2007</td>
<td>7%</td>
<td>56%</td>
<td>12.7%</td>
<td>13.6%</td>
</tr>
<tr>
<td>Downie et al. [27]</td>
<td>Developing countries</td>
<td>1993-2009</td>
<td>6%</td>
<td>8%</td>
<td>25%</td>
<td>2%</td>
</tr>
</tbody>
</table>

**Pseudomonas, Enterobacter, Candida, GBS, Serratia, Acinetobacter and Anaerobes** [11, 20, 23]. The main risk factors associated with LONS are prematurity, central venous catheterization (duration > 10 days), nasal canula, gastrointestinal tract pathology, exposure to antibiotics, and prolonged hospitalization [7, 24]. Didier et al. [25] found three major types of late onset neonatal infections (LONI): *E. coli*-induced urinary tract infection, CONS septicemia affecting preterm infants and severe GBS infections. Other studies are compiled in Table 2.

In spite of the decrease of early-onset GBS sepsis due to the implementation of universal screening and intrapartum prophylaxis, late-onset GBS sepsis remains unchanged, being an important public health problem and associated with a high mortality and morbidity in preterm newborns [25]. This observation is in accordance with the hypothesis that LONS is usually acquired from the environment.

Several studies have related antenatal antibiotic treatment to the increase of antibiotic-resistant cases of LONS, mainly due to *E. coli* [25-28].

To prevent nosocomial infections, it is important that good hand hygiene that has been promoted by several global programs is carried out. Intravascular catheters and the fragile skin of the neonates are important points of entrance for intrahospital microorganisms with the consequent risk of neonatal sepsis [29].

### Symptoms and Diagnosis

The clinical symptoms manifested by neonates with EONS and LONS are non-specific and usually include temperature instability, respiratory problems, apnea, feeding intolerance, etc. [7]. Generally, the diagnosis of neonatal sepsis is diagnosis carried out by blood, CSF and urine cultures. Nowadays, other diagnostic tools such as complete blood cell count, C-reactive protein, procalcitonin, mannose binding lectin, cytokine profile, etc. are being studied. In the case of LONS, acute phase reactants, chemokines and cytokines, and cell-surface antigens are non-specific biomarkers that have been studied for diagnosis and management [30]. More recently, the use of genomics and proteomics are being analyzed for detecting neonatal sepsis. The diagnosis of well-defined neonatal sepsis is difficult due to the high number of negative cultures. For this reason, the term of clinical sepsis has been created based on the symptoms and clinical characteristics presented by the neonate [31].

### Neonatal Sepsis Treatment

Antimicrobial treatment of neonates with suspected sepsis must start immediately after birth and without delay. The isolation and antimicrobial susceptibility tests are not immediately available and results are not obtained in 24 hours. For these reasons, antimicrobial treatment is usually empirical using antibiotics effective against the most likely pathogens [32]. The empirical treatment of EONS consists of ampicillin (Am) and gentamicin (Gm), which cover common pathogens such as GBS, Gram-negative bacteria and Listeria and have synergic action. The combination of ampicillin - cefotaxime is only given in the case of meningitis determined by CSF positivity or by clinical suspicion. In the case of LONS, the therapy must be of extended spectrum antibiotics in order to cover Gram-negative and Gram-positive microorganisms. The duration of antibiotic therapy is of 10 days in EONS without meningitis, 10-14 days in LONS without meningitis, and 14-22 days in the cases of neonatal meningitis. However, an increase in the percentage of Gram-negative bacteria resistant to Am and Gm has been observed [24, 33, 34]. Several studies found that the 75-78% of *E. coli* strains causing EONS were ampicillin-resistant and 19-53% were gentamicin-resistant [24, 33]. In the case of *E. coli* isolates from LONS, between 19-50% were ampicillin-resistant and 9-16% were gentamicin-resistant [24, 33]. This trend has also been observed in developing countries [35]. For these reasons, although the current guidelines for empirical therapy in neonates seem to be appropriate [32], it is necessary to carry out studies about the susceptibility of bacteria causing neonatal sepsis in order to avoid an emergence and/or an increase in resistance levels. After empirical treatment, the choice of the antibiotics depends on the microorganism isolated, their antimicrobial susceptibility and the mechanisms of resistance used by the microorganism.

**Streptococcus agalactiae** or group B *Streptococcus* (GBS) has been the main etiologic agent of early neonatal sepsis in developed countries. In developing countries, this remains to be confirmed, although the few reports available point out that GBS is also a highly prevalent cause of neonatal infections. This microorganism belongs to the gastrointestinal tract microbiota from where it can colonize the vagina. Colonization of a pregnant woman's vagina is very important, as it implies an enhanced risk of GBS being transmitted vertically to the child before or at birth, and subsequently causing infection in the newborn. In Spain, it has been reported that 10-18.5% of pregnant women are colonized by GBS [36]; 22.76% in Tehran [37]; 6% in Iran [38]; 19% in Poland [39]; and 20% in Taiwan [40]. To avoid this enhanced risk of vertical transmission, several diagnostic and prophylactic protocols have been proposed. In 1996, the Center of Disease Control (CDC) recommended taking vaginal and rectal samples from pregnant women in their last antenatal visit and administering a prophylactic antibiotic such as penicillin G or ampicillin during pregnancy or at the time of delivery in women found to be colonized by GBS in antenatal screenings. If the pregnant woman is allergic to betalactamics, erythromycin or clindamycin must be used [41]. When implemented, the use of these prophylactic measures resulted in a decrease in the incidence of infection by GBS. A good example of this success was a study carried out in 10 hospitals of Barcelona (Spain) in which it was found that the incidence of GBS as cause of neonatal sepsis was reduced from 1.92/1,000 newborns in 1994 to 0.26/1,000 newborns in 2001 (p < 0.001) [42]. Another study revealed a decrease in the incidence of GBS vertically transmitted.
neonatal sepsis from 65.4% to 36.4% due to the CDC prophylaxis [43]. Data reported by the CDC showed that after implementation of the guidelines, the incidence of EONS by GBS reduced from 1.7/1000 live births in 1993 to 0.34/1000 live births in 2004 [44].

With intrapartum prophylaxis, the proportion of women exposed to intrapartum antibiotics has doubled [45]. In addition, the incidence of bacterial species causing EONS has changed. Several studies have associated this change in the etiology of EONS with the implementation of GBS prophylaxis. Thus, EONS by GBS has decreased but an increase in the rates of other microorganisms has been reported, mainly E. coli [1, 46, 47] especially in low-birth weight infants [43].

Nonetheless, not only has there been a change in the etiology of EONS been observed but an increase in Am-resistant bacteria causing EONS has also been described [24,33,34]. In the last years, GBS presenting reduced penicillin susceptibility (PRGBS) has been reported [48,49]. The increase in the levels of penicillin resistance has been attributed to the development of pathogen-specific strategies to prevent neonatal sepsis. In addition, studies on antimicrobial resistance of the microorganisms causing neonatal sepsis are needed in order to improve empirical treatment and avoid the emergence of resistances.

**Conclusion**

Neonatal sepsis remains an important but underestimated problem around the world. In spite of intrapartum prophylaxis, epidemiological surveillance of other pathogens causing early-onset neonatal sepsis is needed. The development of pathogen-specific strategies to prevent this infection could be an important diagnostic tool to reduce the cases of early-onset neonatal sepsis. In addition, studies on antimicrobial resistance of the microorganisms causing neonatal sepsis are needed in order to improve empirical treatment and avoid the emergence of resistances.

References