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Infection in late preterm infants

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ABSTRACT

Background: Late preterm (LP) are at higher risk than term infants to develop infections due to their more immature immune system. Little data about the risks and incidence of infection and sepsis in LP are present in literature.
Aims: To evaluate treated infection rates and risk factors for infection in moderate and late preterm infants (gestational age = 32–36 weeks).
Study design: We retrospectively studied a population of 771 moderate and late preterm infants consecutively admitted to our unit from June 2008 to November 2013.
Results: Treated infections were 128, with an incidence of 16.6%; the 90% (n = 115) occurred during the first 72 hours of life. Blood cultures were positive in 22% of cases, umbilical venous catheter cultures were positive in 26% of cases; Coagulase-negative staphylococci were the most frequently isolated pathogens. Patients of the sepsis group had a C-reactive protein (CRP) mean value of 28.27 mg/L and a procalcitonin mean value of 25.3 μg/L. Risk factors for infections were umbilical venous catheter (UVC) insertion (χ^2 = 15.9; $p \leq 0.05$), prophylaxis with antenatal corticosteroids (χ^2 = 16.7; $p \leq 0.05$) and birth by cesarean section, with observed values very similar to the expected values (χ^2 = 15.9; p = 0.1). Respiratory symptoms were found in 47 of the 60 patients in the sepsis group (78.3%).
Conclusions: Late and moderate preterm infants have an increased significant risk of infection compared to term infants. Infections, given the high frequency of negative cultures in neonates, should be often suspected and treated on the basis of clinical features and inflammatory markers, trying always to avoid a possible overtreatment.

1. Introduction

Late preterm (LP) infants are defined as those born at 34 0/7 to 36 6/7 weeks of gestational age (GA); they account for about 74% of all preterm births and 8–9% of total births in the United States [1]. These infants experience the interruption of the normal fetal development during the last six weeks of gestation, a critical period for growth of brain, lungs and other systems development.

Though most LP infants (~80%) will have a neonatal course with no significant complications [2], LP compared with term infants, are at increased risk for resuscitation at birth, feeding difficulties, jaundice, hypoglycemia, temperature instability, apnea and respiratory distress with a threefold higher mortality rate (7.7 vs 2.5 per 1000 live births) [3].

Meanwhile several authors described and investigated these complications in LP infants; still little data about the risks and incidence of infection and sepsis in LP are present in literature.

Preterm infants are at higher risk than term infants to develop infectious diseases due to their more immature immune system. Several risk factors frequently associated with the late preterm birth are also associated with an increased incidence of sepsis: premature rupture of membranes (PROM), prolonged time of premature rupture of membranes, maternal peripartum infections, chorioamnionitis, cesarean section or instrumental delivery and Apgar scores less than 7 at 5 minutes.

The incidence of sepsis in the neonatal period is greater than at any other period of life with values widely depending on population studied: ranging from 1–5 cases per 1000 live births in the developed countries to 49–170 cases per 1000 live births in developing countries [4]. Signs and symptoms of neonatal sepsis are often non-specific, especially in preterm infants and diagnosis is complicated by the frequent presence of non-infectious conditions that resemble those of sepsis. Although the presence of growth of an organism from a sterile site is the “gold standard” for definitive diagnosis, up to 25% of neonates with bacterial sepsis have a low organism burden that would not be detected with culture of smaller blood volumes [5]. Therefore, to identify neonates with suspected infection it must be evaluated the presence of risk factors in combination with clinical history and diagnostic tests results. Risk factors depend on the time of onset of signs or symptoms, reflecting the differing etiologies. Early onset sepsis (EOS) is defined by the onset of signs or symptoms and an associated positive culture at or before 72 hours of life; late onset sepsis (LOS) is characterized by the onset of symptoms at greater than 72 hours of life.

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Evaluation of the cerebrospinal fluid is recommended for infants with suspected sepsis or with blood culture proven bacteremia. Organisms are not isolated from blood in up to 38% infants who have a pathogen isolated from cerebrospinal fluid (CSF) [6]. Urine culture should be used in the evaluation for LOS. Tracheal aspirate culture reflects mainly colonization rather than infection.

The median incidence of blood-culture confirmed sepsis was 16 per 1000 live births (from 2.2 to 9.8 per 1000 live births for EOS and from 20.7 to 50 per 1000 for LOS). The rate of mortality is now 5–20% for EOS, but over 30% in very preterm infants [4].

In addition to blood, CSF and urine culture, laboratory tests may be beneficial in identifying infected neonates and in deciding on duration of antimicrobial therapy. Among these, neutrophil count, immature to total neutrophil ratio, C-reactive protein (CRP) and procalcitonin are the most used. Neutrophil indices have proven most useful for excluding infants without infection rather than for identifying infants with infection [7].

CRP is an acute-phase protein synthesized and secreted by the liver in response to inflammatory cytokines and increases within 6 to 8 hours of infection, with a peak from 24 to 26 hours following infection [8]. Thus has a low sensitivity if measured during the first hours of life and its normal values variates with gestational age [9]. Non infectious processes can also have an elevated CRP up to 10 times the normal concentration.

Procalcitonin is a peptide precursor of the hormone calcitonin whose values appear to increase 2 hours following pathogen exposure, peak within 12 hours and return to baseline levels within 48 to 72 hours. It has better sensitivity but less specificity than CRP for identifying infants with neonatal sepsis [8]. Procalcitonin levels increase physiologically after birth and in others conditions, such as respiratory distress syndrome.

2. Materials and methods

We retrospectively studied a population of 771 infants, both inborn and outborn, consecutively admitted to our unit from June 2008 to November 2013, with a GA between 32 and 36 weeks (GA 32 0/7–36 6/7 weeks). Moderate term infants, with GA of 32 and 33 weeks, were also included along with the LP (34–36 weeks of GA), being a population often not taken into account in many studies focused only on preterms with less than 32 weeks of GA. For all infants who showed at least one clinical, laboratory or bacteriologic finding suggestive for infection the following data were collected and analysed: history of maternal diabetes, use of antenatal corticosteroids, type of delivery, birth weight, Apgar score at 5 minutes, presence of respiratory disease or other symptoms during the hospital stay, insertion of an UVC, values of CRP and procalcitonin at different hours of life, results of cultures, antibiotic treatment.

For each patient results of cultures performed (blood culture for aerobic and anaerobic bacteria, urine culture, bronchoalveolar fluid culture, tip of oro-tracheal tube culture, tip of UVC culture, ear canal swab and pharyngeal swab cultures) have been recorded. Lumbar puncture for CSF culture was not routinely performed in preterm neonates in the period studied.

Rectal and vaginal maternal swabs cultures, being taken usually at 35–37 weeks of gestation, were available only for a limited number of patients, therefore not included in our analysis.

According to the normal values for CRP and procalcitonin for preterm infants published in 2011 by Chiesa et al. [10], have been considered as elevated values of CRP >10 mg/L and values of procalcitonin >10 μg/L. In order to reduce the number of false positivity have been taken into account only procalcitonin levels determined after 24 hours of life.

Patients were classified into four groups based on the clinical, laboratory and bacteriologic findings:

(a) *Sepsis:* presence of clinical signs/symptoms, elevated CRP or procalcitonin levels, positive or negative blood culture (or culture from a deep site);
(b) *Specific infection:* absence of clinical signs/symptoms, presence of elevated CRP or procalcitonin levels, positive blood culture (or positive deep culture or Group B streptococci (GBS) positive swab);
(c) *Non-specific infection or inflammation:* absence of clinical signs/symptoms, elevated CRP or procalcitonin levels and negative cultures;
(d) *Contamination:* absence of clinical signs/symptoms, normal CRP and procalcitonin levels, a positive culture from any site.

Intravenous antibiotics were administered in 86 infants (67% of cases). Ampicillin/sulbactam was the antibiotic used in all patients, alone or in association with amikacin, except in two cases of LOS where vancomycin and metronidazole were added to the first two antibiotics. In two cases of non-bacterial infections, a case of herpes simplex virus (HSV) infection and a case of *Candida* systemic infection, specific treatment was administered (respectively acyclovir and fluconazole).

3. Results

In our population of 771 late to moderate preterm infants, 137 had at least one clinical, laboratory and bacteriologic finding suggestive for infection. Demographic features and risk factors of the 137 infants are shown in Table 1.

Of the 137 cases of suspected infection: 60 (44.2%) were classified as sepsis; 22 (16.2%) as specific infections; 46 (33%) as non-specific infections or inflammation and 9 cases (6.6%) were considered as a contamination, as reported in Table 2. Therefore, excluding the 9 contaminations, the treated infections were 128, with an incidence of 16.6%. The 90% of infections cases ($n=115$) occurred during the first 72 hours of life.

Table 2
Treated infections in moderate and late preterm infants (GA = 32–36 weeks), classified on the basis of the clinical, laboratory and bacteriologic findings.

GA	*n*	Sepsis (*n*)	Specific infection (*n*)	Aspecific infection, inflammation (*n*)	Contamination (*n*)
32	4	3	1	0	0
33	22	7	4	10	1
34	31	18	5	7	1
35	34	10	7	13	4
36	46	22	5	16	3
Total	137	60	22	46	9

Table 1
Demographic features and risk factors of the 137 moderate and late preterm infants (GA = 32–36 weeks) studied.

GA	*n*	Mean birth weight (g)	Mean Apgar at 5 min	Maternal diabetes (*n*)	Antenatal corticosteroids (*n*)	PROM (*n*)	Cesarean section (*n*)	IUGR/SGA (*n*)	UVC (*n*)
32	4	1710	8	2	2	0	4	1	4
33	22	1916	8.6	1	12	4	18	5	14
34	31	2085	7.8	7	16	2	23	3	14
35	34	2409	8.7	2	10	5	21	2	8
36	46	2623	8.9	1	4	1	32	5	16