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Neonatal sepsis: Epidemiology and comparison between preterm and term newborns

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ABSTRACT

Introduction: Neonatal sepsis is a severe clinical syndrome that continues to be a common and significant health care burden. Knowledge of the local epidemiology allows for a better empirical treatment and improves morbidity and mortality. The aim of this study was to determine the prevalence, epidemiology, and etiology of blood culture-proven sepsis in neonates and to determine whether there are differences between preterm and term newborns.
Methods: A retrospective study was carried out in a tertiary hospital in Madrid, Spain, during 2021, including 1443 patients at risk of developing sepsis.
Results: The majority of sepsis episodes occurred in preterm newborns (64.81%) and most of them were very low birth weight infants (74.29%). Late-onset sepsis represented 94.92% of all the episodes reported with an incidence of 11.4 (95% CI 8.8–14.8) per 1000 live newborns. Early onset sepsis incidence was 0.6 (95% CI 0.2–1.8) per 1000 live newborns. Coagulase-negative staphylococci took the first place as causative agents of sepsis (66.10%), causing in all the episodes late onset catheter-related bloodstream infection. When the newborns who developed sepsis were compared with those who did not developed sepsis, the presence of venous/arterial access device was significantly associated with sepsis in both preterm (odds ratio (OR) 8.12, 95% CI 0.47–141.40) and term newborns (OR 16.58, 95% CI 1.00–275.20). Recent surgery was nevertheless the main risk factor in term newborns (OR 45.29, 95% CI 13.70–149.70). Among those patients who developed sepsis, no differences between preterm and term newborns were found regarding time onset, mechanism of transmission, etiological agents, and mortality. A 100% of the preterm and 42.11% of the term newborns presented two or more risk factors. The mortality rate observed here has been 1.85% (95% CI 0.33–9.77%).
Conclusion: The main risk factors for sepsis were venous/arterial access device (for both preterm and term newborns) and recent surgery (term newborns). Prematurity and being a catheter carrier were strongly associated with late-onset neonatal sepsis, mainly due to coagulase-negative staphylococci. The mortality rate was lower than that observed in other high-income countries.

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Sepsis neonatal: epidemiología y comparación entre recién nacidos prematuros y a término

Palabras clave:
Sepsis
Recién nacido prematuro
Epidemiología

RESUMEN

Introducción: La sepsis neonatal es un cuadro clínico grave y frecuente. El conocimiento de la epidemiología local permite un mejor tratamiento empírico y reducir la morbilidad y mortalidad. El objetivo de este estudio es determinar la prevalencia, la etiología y la epidemiología de la sepsis en los neonatos, y analizar si hay diferencias entre los recién nacidos prematuros y a término.

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Métodos: Se ha llevado a cabo un estudio retrospectivo en un hospital terciario de la Comunidad de Madrid, España, en el año 2021, incluyendo a 1.443 pacientes en riesgo de desarrollar sepsis.
Resultados: La mayoría de los episodios de sepsis neonatal han ocurrido en recién nacidos prematuros (64,81%), y gran parte de ellos eran de muy bajo peso (74,29%). La sepsis de inicio tardío ha representado el 94,92% de todos los episodios, con una incidencia de 11,4 (IC 95%: 8,8-14,8) por cada 1.000 nacidos vivos. La incidencia de la sepsis de inicio precoz ha sido de 0,6 (IC 95%: 0,2-1,8) por cada 1.000 nacidos vivos. Los estafilococos coagulasa negativa han sido los principales agentes causales (66,10%) dando lugar todos ellos a sepsis de inicio tardío asociadas a catéter. Los resultados de este estudio sugieren que ser portador de catéter está asociado de forma significativa al desarrollo de sepsis, tanto en recién nacidos prematuros (*odds ratio* [OR]: 8,12; IC 95%: 0,47-141,40) como en los a término (OR: 16,58; IC 95%: 1,00-275,20). Además, en los pacientes que han desarrollado sepsis, no se han detectado diferencias estadísticamente significativas entre ambos grupos en cuanto al tiempo de inicio, el mecanismo de transmisión, la etiología y la mortalidad. El 100% de los prematuros y el 42,11% de los a término presentaron 2 o más factores de riesgo. La mortalidad observada en este estudio ha sido del 1,85% (IC 95%: 0,33-9,77%).
Conclusión: Los principales factores de riesgo para desarrollar sepsis han sido ser portador de catéter (prematuros y a término) y la cirugía reciente (a término). La prematuridad y el ser portador de catéter se han asociado fuertemente a sepsis neonatal de inicio tardío, principalmente por estafilococos coagulasa negativa. La mortalidad ha sido inferior a la observada en otros países de altos ingresos.
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Introduction

Sepsis can result from systemic inflammatory responses. It is a serious condition in which proinflammatory cytokines (mainly IL-1, IL-6 and TNF-alpha) are hyperproduced in response to an infection and cause organ damage although their initial purpose was to induce systemic protective effects. Among these protective actions are an increase in body temperature, acute phase protein synthesis and leukocyte production through different colony-stimulating factors. Early signs and symptoms are usually nonspecific and may include irritability, poor feeding or lethargy. Others such as respiratory distress, neurological alterations or digestive symptoms might be present. Eventually, sepsis may progress to septic shock which is reached when these symptoms are accompanied by hyperlactataemia, hypotension requiring vasopressor therapy and potentially disseminated intravascular coagulation.[1,2]

Neonatal sepsis is common and potentially fatal. Recent systematic reviews and meta-analysis estimate a global incidence of 3930 neonatal sepsis cases per 100 000 live births (95% CI 1937–7812).[3] Up to 24% of neonatal deaths can be attributed to sepsis according to the literature.[4] The term neonatal sepsis is used when the infection occurs within the first 29 days of life and can be classified into two categories based on the time of presentation after birth: early-onset sepsis (EOS) when occurring in the first 72 h of life and late-onset sepsis (LOS) occurring after this time period. According to the mechanism of transmission, neonatal sepsis is divided into three groups: vertical transmission sepsis, nosocomial sepsis, and community-acquired sepsis. Vertical-transmission sepsis usually is EOS, whereas nosocomial and community sepsis frequently are LOS.[5]

Microorganisms causing EOS are typically colonizers of the maternal rectum or genitourinary tract, reaching the fetus during labor or intrapartum. Other microorganisms, such as *Listeria monocytogenes* can reach the fetus by transplacental transmission due to the ingestion of contaminated water or food during pregnancy. Nosocomial sepsis typically presents horizontal transmission and is caused by pathogens from hospital employees or microorganisms located at the neonatal unit or those belonging to the new-born microbiota.[6,7]

There are several factors that can lead to an increased risk of developing neonatal sepsis. Among risk factors for EOS the most important ones are: prematurity (gestational age less than 37 weeks), intra-amniotic infection (chorioamnionitis), maternal fever during delivery (higher than 38 °C), prolonged (longer than 18 h) or premature rupture of membranes and maternal group B streptococcal (GBS) colonization.[7] Specific risk factors for LOS are: breakage of natural barriers (skin and mucosa), prolonged use of venous/arterial access device, invasive procedures (surgery, endotracheal intubation, gastrostomy among others), and prolonged use of antibiotics.[7,8]

Antibiotic therapy should be started as soon as sepsis is suspected and may vary according to local epidemiology. With reference to vertical transmission sepsis, empiric treatment frequently includes a combination of intravenous ampicillin and gentamicin, or ampicillin and cefotaxime if meningitis is suspected, in order to cover for the most common pathogens. For nosocomial sepsis, coverage for *Staphylococcus aureus*, coagulase-negative Staphylococci (CoNS) and Gram negative pathogens (such as *Pseudomonas* or *Klebsiella* species) must be provided.[9]

In this study, our main objective was to determine the prevalence, etiology, and epidemiology of blood culture-proven sepsis in neonates and to figure out whether there are differences between preterm and term newborns.

Materials and methods

A retrospective study was carried out in a tertiary hospital in Madrid, Spain, during 2021. All newborns admitted to general neonatal unit and intensive care unit during this time period were included in the study. At our hospital the number of beds available in the Neonatal Unit is 73. Additionally, the hospital has a 23-bed Neonatal Intensive Care Unit. In 2021, 4893 births were reported at our hospital and approximately 9.3% of the newborns were preterm infants.

The onset of sepsis was defined by the date of blood culture collection. Neonatal sepsis was diagnosed when the patient met the following criteria: presenting one or more symptoms compatible with sepsis, elevated acute-phase reactants (C-reactive protein and procalcitonin), blood count alterations (i.e. leukocytosis, leukopenia, thrombocytopenia or altered ratio of immature to total neutrophils), along with positive blood culture, according to the literature.[10] Considering the time of presentation after birth, sepsis was classified into two categories: early-onset sepsis (EOS) when occurring in the first 72 h of life and late-onset sepsis (LOS) occurring after this time period.

The incidence of neonatal sepsis has been calculated with the population at risk of developing sepsis. The patients at risk of developing sepsis have been those for whom blood cultures were performed (a total of 1443 patients). At our hospital blood cultures are obtained as part of the evaluation of an already-diagnosed infectious disease with potential to cause sepsis due to its complicated nature or difficult control, or as part of the initial assessment of a patient with both clinical and analytical parameters compatible with sepsis.

In this study, single aerobic pediatric blood culture bottles were obtained from each patient. Although the blood volume extracted from each patient should have been 5 mL, it was not always possible as some of the patients were preterm newborns with very low birth weight.

The interpretation of a positive blood culture as a true bacteremia or contamination has been carried out with the collaboration between the microbiologist and the physician. The following criteria were taken into account: number of blood cultures positive for the same microorganism, time to growth, the clinical status of the patient, clinical evidence of infection, the presence of foreign device, and administration of previous antibiotic therapy.[11] Both central and peripheral venous/arterial catheter have been considered as vascular access device. Specifically, the minimum exposure time to the device before developing sepsis considered here has been 48 h, according to the literature.[12] When CoNS were isolated, to be interpreted as a true bacteremia, the patient was required to have not only symptoms compatible with sepsis but also to have at least two positive blood cultures for the same microorganisms.[13] Septic shock was reached when sepsis symptoms were accompanied by severe hypotension requiring vasopressor therapy.[14]

Blood culture incubation was carried out on BD BACTEC™ FX (BD, USA) for up to five days at 37 °C until they were identified as positive. These flasks were evaluated with the Bruker MALDI-biotyper system of Bruker DaltoniK (Bruker Daltonik GmbH, Bremen, Germany) for direct microorganism identification following the protocol reported and validated by García-Clemente et al.[15] After identification, antimicrobial susceptibility testing was carried out following the procedure previously published.[16] A Gram stain was performed with the positive flasks, and they were also subcultured on TSA blood agar with ram blood (Thermo Scientific™, USA) and chocolate agar (Thermo Scientific™, USA), which both were incubated at 37 °C with 5% CO_2 for 24 h.

With reference to statistical analysis, qualitative variables were expressed as absolute and relative frequencies and were compared, and their association was studied, using Pearson's Chi-squared test with Yates's continuity correction or Fisher's exact test, as appropriate. When one of the elements of the 2×2 contingency table was 0, Mid-*P* exact test was calculated instead of the above-mentioned tests and, consequently, Mid-*P* exact *P*-value (two-sided) was considered and shown. Also in these cases, the odd ratios were calculated with Haldane–Anscombe correction. Quantitative variables were expressed as median (interquartile range, IQR) and were compared using Mann–Whitney *U* test. Statistical analyses were done using R (https://cran.r-project.org) and OpenEpi (http://www.OpenEpi.com). Two-sided *P*-value < 0.05 were considered significant.

Results

During the 12-month study period, 1443 newborns were identified at risk of developing sepsis. Specifically, 54 of them suffered at least one episode of sepsis. The incidence of sepsis observed in this study was 11.04 cases per 1000 live newborns (95% CI 8.47–14.37). According to the time onset of sepsis, the incidence of EOS was 0.61 cases per 1000 live newborns (95% CI 0.2–1.8) and 11.4 cases per 1000 live newborns (95% CI 8.8–14.8) for LOS.

The case fatality rate was 1.1% for the population at risk and 1.85% (95% CI 0.33–9.77%) for the newborns who developed sepsis, with a risk of mortality of 0.07%.

Among the 54 patients who developed sepsis, 35 (64.81%) were preterm newborns, as can be seen in Table 1. With reference to sex, 26 were male infants (48.15%) and no statistically significant differences has been evidenced between preterm and term newborns regarding sex. Median gestational age was 31 (IQR = 10) weeks and median birth weight was 1610 grams (IQR = 1709.25). Among the 35 preterm patients, 26 (74.29%) were considered of very low weight (<1.5 kg).

With reference to the risk factors, the presence of venous/arterial access device was the most frequent one, being present in all the septic patients. The practice of invasive proce-

Table 1
Epidemiology of neonatal sepsis in this study.

	All patients (*n* = 54)	Preterm newborns (*n* = 35)	Term newborns (*n* = 19)	*P*-value[a]
Sex				
Male *n* (%)	26 (48.15)	19 (54.29)	7 (36.84)	0.347
Median gestational age in weeks (IQR)	31 (10)	28 (4)	38 (2)	–
Median birth weight in grams (IQR)	1610 (1709.25)	1000 (723.50)	2785 (815)	–
Risk factors				
Type of risk factors				
Venous/arterial access device *n* (%)	54 (100)	35 (100)	19 (100)	ND
Recent surgery *n* (%)	9 (16.67)	4 (11.43)	5 (26.32)	0.251
Immunosupression therapy *n* (%)	2 (3.70)	1 (2.86)	1 (5.26)	> 0.999
Parenteral nutrition *n* (%)	3 (5.55)	2 (5.71)	1 (5.26)	> 0.999
Maternal GBS colonization n/total (%)	4/44 (9.09)	0/26 (0)	4/18 (22.22)	0.045
Invasive procedure[b] *n* (%)	12 (22.22)	10 (28.57)	2 (10.53)	0.178
Chorioamnionitis *n* (%)	0	0	0	ND
Congenital medical conditions *n* (%)	1 (1.85)	0	1 (5.26)	0.352
Number of risk factors per patient				
Only 1 factor *n* (%)	11 (20.37)	0	11 (57.89)	< 0.001
Only 2 factors *n* (%)	28 (51.85)	21 (60.00)	7 (36.84)	0.1795
Only 3 factors *n* (%)	13 (24.07)	12 (34.29)	1 (5.26)	0.03128
Case fatality *n* (%)	1 (1.85)	1 (2.86)	0	> 0.999

GBS: group B streptococcus.

[a] The *P*-values obtained after analyzing differences in percentages between preterm and term newborns for each variable are indicated (Chi-squared test or Fisher's exact test, as appropriate). ND: not determined when a 100% or a 0% is present in both groups.

[b] Risk factors for the development of neonatal sepsis taken into account as "invasive procedures" were the following: mechanical ventilation, ostomies and surgical drains.

Table 2
Risk factors associated to sepsis and risk estimates (odds ratio) in preterm newborns who underwent a blood culture.

Risk factor	Number of cases (percentage)				
	Sepsis ($n=35$)	NO sepsis ($n=111$)	*P*-value	OR[a]	95%CI
Venous/arterial access device	35 (100)	100 (90.09)	0.043[b]	8.12	0.47–141.40
Recent surgery	4 (11.43)	5 (4.50)	0.281[c]	2.74	0.69–10.81
Immunosupression therapy[d]	1 (2.86)	ND	ND	ND	ND
Parenteral nutrition	2 (5.71)	6 (5.41)	>0.999[c]	1.06	0.20–5.51
Maternal GBS	0	1 (0.90)	0.760[b]	ND	ND
Invasive procedure	10 (28.57)	19 (17.12)	0.14 (0.219[c])	1.94	0.80–4.69
Chorioamnionitis	0	1 (0.90)	0.760[b]	ND	ND
Congenital medical conditions	0	1 (0.90)	0.760[b]	ND	ND

ND: not determined.
[a] OR is shown when at least one case of sepsis is present.
[b] Mid-*P* exact test.
[c] Fisher's exact test.
[d] Data of immunosuppression therapy could not be collected for preterm newborns who did not developed sepsis.

dures was the second most common risk factor, observed in 22.22% of the newborn infants, as depicted in Table 1. Screening for maternal GBS colonization could be performed in 44 out of 54 pregnant women, the other ten patients did not show pregnancy follow-up at our hospital and this data could not be collected. Among the 44 pregnant women screened, only 4 (9.09%) were positive for GBS colonization. Maternal GBS colonization has been less frequent in preterm newborn than in term infants. Chorioamnionitis was the less frequent risk factor reported in this study as none of the patients was born from a mother with this infection. As to the number of risk factors presented per patient, the majority of the newborns, specifically 28 (51.85%), showed two risk factors. The number increases in preterm newborn showing all of them at least two factors (Table 1).

With respect to case fatality, only one death caused by a respiratory tract infection was reported in a preterm newborn who presented severe congenital medical conditions, leading to a total mortality rate of 1.85%. Consequently, differences in mortality between preterm and term infants were not statistically significant.

With reference to the 1389 newborns who did not developed sepsis, 111 (8%) were preterm infants and regarding the risk factors, venous/arterial access device was the most frequently detected (71.8%). This risk factor was also the most prevalent in both preterm and term newborns who did not develop sepsis, being present in 90.2% and 70.2% of them, respectively.

When the frequencies of the risk factors were compared between the patients who developed sepsis and those who did not developed sepsis, statistically significant differences were detected for the following factors: presence of venous/arterial access device ($P<0.001$), recent surgery ($P<0.001$) and invasive procedures ($P=0.003$). The three factors were more frequent in patients who developed sepsis. When the risk factors were compared between groups, only the presence of venous/arterial access device was significantly associated with sepsis in both preterm ($P=0.043$) and term newborns ($P=0.001$) at the same time, as can be seen in Tables 2 and 3.

Tables 2 and 3 show the risk estimates (odds ratio) of risk factors associated with sepsis.

As for the patients who developed sepsis, nosocomial sepsis represented the most frequent mechanism of transmission in both preterm and term patients accounting for 98.31% of all episodes, as shown in Table 4. Regarding sepsis time onset, LOS was reported in 56 cases (94.92%), reporting only 3 episodes of EOS, two of them caused by *Escherichia coli* and one caused by *Streptococcus agalactiae*. No significant differences were detected between preterm and term newborns with reference to the mechanism of transmission and time onset.

Catheter-related bloodstream infection (CRBSI) was the most common clinical presentation of sepsis, accounting for 40 (67.8%) of all episodes, followed by primary bloodstream infection (BSI) and abdominal-related infection, with an absolute frequency of 15.25% and 8.47% respectively. As can be seen in Table 4, the frequency of CRBSI in term newborns was significantly higher than in preterm newborns (89.47% and 57.5%, respectively). With reference to etiological agents of sepsis, 58 out of 59 episodes reported have been monomicrobial and just one was polymicrobial (caused by *Serratia marcescens* and *Pseudomonas aeruginosa*).

As shown in Table 4, the microorganisms most frequently involved in neonatal sepsis were Gram-positive bacteria, being responsible for 79.66% of all the episodes, specifically 30 out of 40 episodes in preterm newborns (75%) and 17 out of 19 in term infants (89.47%). Coagulase-negative Staphylococci were the leading pathogens, being involved in 66.10% of total episodes. Gram-negative bacteria were reported in 13 out of 59 (22.03%) episodes, with *S. marcescens* (8.47%) followed by *E. coli* (6.78%) as the most common Gram-negative microorganisms. No statistically significant differences were detected between preterm and term newborns with reference to the site of infection and pathogens, except for the CRBSI mentioned before. The incidence of neonatal sepsis excluding cases of coagulase-negative Staphylococci was 4.09 cases per 1000 live newborns (95% CI 2.65–6.31).

Lumbar punction (LP) was performed to obtain cerebrospinal fluid (CSF) to rule out the presence of meningitis in 15 episodes (25.42%) from 12 patients. The majority of LP (10 out of 15) were carried out in preterm newborns, however, differences between groups were not statistically significant. There was only one positive sample in which an *E. coli* was detected in CSF from a preterm patient with a blood-culture proven sepsis caused by the same microorganism.

Finally, septic shock was reached in only 4 episodes (6.78%) reported in 4 patients, all of them in preterm newborns.

Discussion

The majority of our neonatal sepsis episodes was found in preterm newborns, and almost two third of them were very low birth weight infants. This might be, at least in part, consequence of immature immune response. It is clearly established that maternal IgG antibodies are crucial for newborn infants during the first months of life to have an efficient immune response against common pathogens, in particular extracellular bacteria. Transplacental transmission of these antibodies occurs mainly after the 34th week of gestation, when a specific IgG receptor (the so called Neonatal Fc Receptor) is expressed in the syncytiotrophoblast cell layer.[17]

Table 3
Risk factors associated to sepsis and risk estimates (odds ratio) in term newborns who underwent a blood culture.

Risk factor	Number of cases (percentage)				
	Sepsis ($n = 19$)	NO sepsis ($n = 1278$)	*P*-value	OR[a]	95%CI
Venous/arterial access device	19 (100)	897 (70.19)	0.001[b]	16.58	0.99–275.20
Recent surgery	5 (26.32)	10 (0.78)	<0.001[c]	45.29	13.70–149.70
Immunosupression therapy[d]	1 (5.26)	ND	ND	ND	ND
Parenteral nutrition	1 (5.26)	52 (4.07)	>0.999[c]	1.31	0.17–9.99
Maternal GBS	4/18 (22.22)	255 (19.95)	>0.999[c]	1.07	0.35–3.25
Invasive procedure	2 (10.53)	110 (8.61)	0.997[c]	1.25	0.28–5.48
Chorioamnionitis	0	2 (0.16)	0.971[b]	ND	ND
Congenital medical conditions	1 (5.26)	49 (3.83)	0.693[b]	1.39	0.18–10.65

ND: Not determined.
[a] OR is shown when at least one case of sepsis is present.
[b] Mid-*P* exact test.
[c] Fisher's exact test.
[d] Data of immunosuppression therapy could not be collected for term newborns who did not developed sepsis.

Table 4
Clinical characteristics of patients with neonatal sepsis included in the study and pathogens involved.

	All episodes ($n = 59$)	Episodes in preterm newborns ($n = 40$)	Episodes in term newborns ($n = 19$)	*P*-value[a]
Mechanism of transmission				
Vertical transmission sepsis *n* (%)	1 (1.69)	0	1 (5.26)	0.6441
Nosocomial sepsis *n* (%)	58 (98.31)	40 (100)	18 (94.74)	0.6441
Time onset				
EOS *n* (%)	3 (5.08)	1 (2.50)	2 (10.53)	0.4804
LOS *n* (%)	56 (94.92)	39 (97.50)	17 (89.47)	0.4804
Site of infection				
CRBSI *n* (%)	40 (67.80)	23 (57.50)	17 (89.47)	0.0249
Skin and soft tissue *n* (%)	1 (1.69)	0	1 (5.26)	0.644
Abdominal *n* (%)	5 (8.47)	5 (12.50)	0	0.2629
Respiratory *n* (%)	3 (5.08)	3 (7.50)	0	0.6078
Primary BSI *n* (%)	9 (15.25)	7 (17.50)	2 (10.53)	0.7835
Maternal *n* (%)	1 (1.69)	0	1 (5.26)	0.6441
Pathogens				
Gram-positive bacteria *n* (%)	47 (79.66)	30 (75.00)	17 (89.47)	0.3474
Coagulase negative Staphylococci *n* (%)	39 (66.10)	24 (60.00)	15 (78.95)	0.2516
S. aureus n (%)	3 (5.08)	2 (5.00)	1 (5.26)	>0.999
E. faecalis n (%)	4 (6.78)	4 (10.00)	0	0.4016
S. agalactiae n (%)	1 (1.69)	0	1 (5.26)	0.6414
Gram-negative bacteria *n* (%)	13 (22.03)	11 (27.50)	2 (10.53)	0.2537
S. marcescens n (%)	5 (8.47)	5 (12.50)	0	0.2629
E. coli n (%)	4 (6.78)	3 (7.50)	1 (5.26)	>0.999
P. aeruginosa n (%)	2 (3.39)	2 (5.00)	0	0.9117
K. pneumoniae n (%)	1 (1.69)	0	1 (5.26)	0.6414
C. koseri n (%)	1 (1.69)	1 (2.50)	0	>0.999
Lumbar punction for CSF n (%)	15 (25.42)	10 (25.00)	5 (26.32)	>0.999
Septic shock n (%)	4 (6.78)	4 (10)	0	0.4016

[a] The *P*-values obtained after analyzing differences in percentages between preterm and term newborns for each variable are indicated (Chi-squared test or Fisher's exact test, as appropriate). ND: not determined when a 100% or a 0% is present in both groups.
EOS: early-onset sepsis; LOS: late-onset sepsis; CRBSI: catheter-related bloodstream infection; BSI: bloodstream infection.

Hence, preterm infants may have decreased maternal IgG titters, leading to humoral immunodepression. It has also been reported in the literature that relationship between newborn's IgG levels and birth weight is directly proportional. This would explain why low-weight and very-low-weight newborns exhibit a deficient humoral immune system when compared to normal weight infants.[17] And also justifies, at least partially, why the lower the birth weight, the more frequently neonatal sepsis is reported, which has been evidenced in our study and also in others carried out in high-income and middle-income countries.[3,7,18–20]

According to the literature, male newborn infants are at increased risk of developing sepsis compared to female.[21–24] In our study, however, no significant differences in the number of sepsis cases between sex have been noticed.

When the epidemiology of neonatal sepsis is analyzed in high-income and middle-income countries, LOS is generally more frequent than EOS. In our results, not only LOS has been the most common manifestation of neonatal sepsis (94.92%) but also EOS has been reported less frequently than in other studies, representing just 5.08% of all neonatal sepsis cases observed. When the incidence of neonatal sepsis was compared with that reported in high income countries, the incidence of LOS observed here showed to be higher, although the incidence of EOS remained approximately similar.[19,20,25,26] According to the World Health Organization, EOS is indicative of underlying issues of quality of care, such as inconsistent use of preventive measures, like detection of infection in the mother and preventive treatment of the neonate, delayed diagnosis, and poor management of infection and its complications.[27] The low number of EOS cases in the study presented here might have been achieved through identification and taking control over the risk factors for EOS. Among such factors are: screening for GBS colonization during pregnancy, intrapartum antibiotic prophylaxis

if necessary, close clinical surveillance during pregnancy to avoid chorioamnionitis, and repeated observations in infants with risk factors for sepsis in order to start antibiotic treatment as soon as possible whether sepsis is suspected.[28,29]

As reported in the literature, LOS often shows horizontal transmission from nosocomial sources whereas, in the case of EOS, vertical transmission is the most frequent way of pathogen acquisition,[7] which was not a trend observed in our study probably due to the low number of EOS cases.

With reference to etiologic agents and site of infection, our results corroborate those previously found in other studies, where Gram positive bacteria takes the first place as causative organisms of LOS, with CoNS as the leading pathogens, especially in patients with catheters.[7,18,25,26,30] In our study CoNS were responsible for 66.10% of neonatal sepsis cases, all of them leading to late onset catheter-related bloodstream infection (CRBSI in Table 2), being detected in all cases growth of the microorganism in the catheter. It is important to underline here that, in this study, the presence of venous/arterial access device has been associated with the development of sepsis in both preterm and term newborns. Although OR values themselves suggests linkage (Tables 2 and 3), their confidence intervals are wide, including the null value of 1, and consequently, any conclusion about a possible relationship should be taken with caution and is debatable. As is well known, central/peripheral line devices can be easily colonized by microorganisms from skin microbiota. Migration toward the intravascular space can lead to bacteremia and potentially sepsis, giving place to increased length of hospital stay,[31] increased cost[32] and higher morbidity and mortality.[33] Despite appropriate insertion with aseptic techniques, optimal catheter care and removal of nonessential catheters by trained healthcare personnel, CRBSI is likely to happen in patients showing an immature immune system and underdeveloped skin and mucosal barriers, as happens in the preterm newborn infants included in this study. It is important to underline here that, although the presence of venous/arterial access device showed the high OR values mentioned in both preterm and term newborns, recent surgery presented the highest OR value in term newborns (Table 3). This could be due to the fact that all the newborns undergoing surgery are venous/arterial access device carriers.

As shown in Table 1, CoNS were followed by Gram-negative bacteria as the second most frequently detected group of microorganisms, with *S. marcescens* and *E. coli* as the leading pathogens. This result contrasts with other epidemiological studies, where *E. coli* is usually the first Gram negative etiological agent of sepsis.[7,18,25,30] This difference is explained due to a *S. marcescens* outbreak reported in the neonatal unit during the study period. The three EOS cases observed in our study were caused by *E. coli* and *S. agalactiae*, which are the most frequent etiological agents of EOS reported in the literature.[7,18,25,26]

Among pediatric patients affected by invasive fungal disease (IFD), newborn infants represent an important group. In a retrospective multicenter European study that included 1395 episodes of pediatric candidemia, up to 36.4% of the episodes occurred in neonates, and most of them were admitted at the neonatal intensive care unit.[34] Interestingly, no episodes of IFD have been detected in our study. This is due to the practice of preventive measures performed at our hospital, such as: central line care, antimicrobial stewardship and administration of antifungal prophylaxis with fluconazole in those newborns at risk of developing candidemia.

Regarding the risk factors, all patients showed at least one factor that consisted in the presence of central/peripheral catheter. In the preterm newborns group, the practice of invasive procedures (either mechanical ventilation, ostomies or surgical drains) was the second most common risk factor (28.57%), whereas, in the term infants' group, central/peripheral catheter was followed by recent surgery as the second most frequent risk factor (26.32%). Overall, the preterm group of patients showed more risk factors than the term group. Maternal associated risk factors were much less frequent, with only 4 pregnant women with GBS colonization (all in the term newborns group), and none of the 54 mothers developed chorioamnionitis, probably as a result of the close clinical surveillance during pregnancy and intrapartum antibiotic prophylaxis when GBS colonization was present. The most common risk factors evidenced in this study are also the most frequent ones among other neonatal sepsis studies.[25,30,35,36]

The performance of LP in order to obtain CSF in neonates with suspected sepsis is controversial. According to the literature, some authors consider that the threshold for obtaining CSF should be very low in neonates who have a clinical status suggestive of sepsis because up to 23% of neonates with bacteremia will also have concomitant meningitis.[37,38] In our group of patients LP was only performed when the newborn showed clinically considered meningitis, trying to avoid this invasive procedure if not strictly necessary. Meningitis was suspected when at least one of the following symptoms was present: nuchal rigidity, lethargy, seizures, tremors and/or fever.[39] In some cases, performance of lumbar punction might has been restricted due to prematurity or body weight, as lower gestational age and very low birth weight are significantly associated with adverse events during LP such as SpO_2 desaturation.[40]

With reference to septic shock, a low number of cases have been evidenced in this study. It is important to underline here that the majority of the sepsis cases reported have been caused by CoNS, which rarely lead to septic shock.[41]

Regarding mortality, we have observed in this study a rate of 1.85% (95% CI 0.33–9.77%). In this regard, the global mortality for neonatal sepsis, estimated by systematic reviews and meta-analysis, ranges between 17.6% (95% CI 10.30–28.60%)[3] and 18% (95% CI 17–19%).[42] More precisely, if estimated from case-series in developed countries, mortality averages 12% with 95% CI 11–13%.[19,25,26,42,43] Although our mortality rate seems to be remarkably lower, additional studies with an increased number of patients are needed to confirm it.

The limitations of our study include the retrospective nature and the low number of patients included, which directly affects its statistical power. This limitation should be taken into account in all the considerations along this manuscript regarding the presence or absence of statistically significant differences between groups or association between variables. Additionally, the patients were required to have positive blood cultures to be included in this study. It must be taken into account that the profitability of this technique can be affected by some factors, such as the initiation of the antimicrobial treatment before the extraction of the blood culture or the low volume of blood inoculated, leading to a false negative result and the subsequent exclusion of the patient from this study. Moreover, it is important to underline here that some microorganisms, such as genital mycoplasmas (*Mycoplasma hominis*, *Ureaplasma urealyticum* and *Ureplasma parvum*) show a deficient growth in blood culture bottles. For this reason, the infants born from women with subclinical chorioamnionitis caused by these microorganisms might have not been diagnosed of blood culture proven sepsis and, therefore, not included.

In conclusion, the epidemiological data from our study shows some similarities with others carried out in high-income countries. Firstly, LOS has been more frequently reported than EOS. Secondly, CoNS took the first place as causative agents of sepsis, associated mainly to CRBSI, and thirdly, the majority of patients were premature newborn infants, most of them showing very low birth weight. The results of this study suggest that the presence of venous/arterial access device is significantly associated with sepsis

in both preterm and term newborns (OR > 8), and recent surgery is associated with sepsis in term newborns (OR > 45). Among those patients who developed sepsis, no differences between preterm and term newborns were found regarding time onset, mechanism of transmission, etiological agents, and mortality. The number of risk factors was significantly higher in the preterm group. The mortality rate observed here has been apparently lower than that observed in high-income countries. Further studies with a higher number of patients and consequently more statistical power are required to add additional evidence to these results and increase the knowledge about neonatal sepsis in both preterm and term newborns.

Ethics approval

This is a retrospective study and no ethical approval is required.

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Authors' contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Eduardo Rubio-Mora. The first draft of the manuscript was written by Eduardo Rubio-Mora, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Consent to participate

No informed consent was needed.

Consent to publish

No informed consent was needed.

Conflict of interests

The authors have no relevant financial or non-financial interests to disclose.

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